U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

Eighth Meeting

Friday,
October 20, 2005

Brookside Room A/B
Marriott Bethesda North Hotel and
Montgomery County Conference Center
5701 Marinelli Road
North Bethesda, Maryland

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C O N T E N T S

P R O C E E D I N G S (8:33 a.m.)

MS. BERRY: Good morning. In keeping with our new tradition of reviewing military history, I'll tell you that today, on this day in 1944, keeping his "I shall return" pledge to the people of the Philippines, General Douglas MacArthur waded ashore, and just like General MacArthur, the SACGHS has returned on its second day of our October meeting.

(Laughter.)

DR. EVANS: Hopefully there will be less carnage.

(Laughter.)

MS. BERRY: Yes, a lot less carnage.

Sort of a clean-up item to begin with. Yesterday we mentioned the coverage and reimbursement report and the recommendations that were edited and distributed to you.

There was the original version, and then the edited version, members of the committee were supposed to take a look at those. What we're going to do is not have a protracted discussion and try to edit and reedit, because that just takes too long. What we'll have is essentially an up or down vote.

Will we accept the staff recommendations for some of the editorial comments, the green-line version that you have? Yes or no? If it's no, we will go back to the original language that the committee approved at our last meeting.

So we'll just go around the room. Do we have everybody here? Yes, I think so.

So the question will be on approval of the edited version of the recommendations for the Coverage and Reimbursement Task Force, the green-line version that you all have.

I guess we'll start with Jim.

DR. EVANS: I vote for approving the edited version.

MS. BERRY: Chira?

MS. CHEN: I would do the same.

DR. FITZGERALD: Yes to the edited.

MS. BERRY: Agnes?

MS. MASNY: I would say yes to the edited. The only thing is I do have a question, sort of a concern that came up to me, especially in view of yesterday's discussion. That is for item number seven, just a clarification point where we say genetic counseling to be able to provide full access of genetic counseling services for all Americans, and then it goes on to identify a body who would oversee to determine who is appropriate to provide this kind of counseling.

I think that, and I don't know if the committee would like to look at using the word not just "genomic," but "genetic counseling." I think that if we leave just genetic counseling, I think genetic counseling implies specifically genetic counseling for single-gene disorders, and I think the information that we heard, specific profession and a specific specialty.

I think with the information that we heard yesterday, that we need to have prepared health professionals who will be able to provide and possibly bill for genetic, genomic counseling, and education services. So I just think that we should have a little bit of foresight. I don't know if the task force would want to address that, or if in fact this was just intended for genetic counseling.

MS. BERRY: Suzanne?

MS. GOODWIN: You guys don't have a full copy of the report, but at the beginning, we had, at your request, added some definitions of some of the terminology used throughout the report. I don't know if you want to expand the definition throughout the report to whenever the term "genetic counseling services" is used to say "genetic and genomic counseling," or to simply say "genetic counseling services and make sure that the definition included at the beginning of the report encompasses both what you just described, genetic and genomic counseling services.

MS. MASNY: Maybe if we, as you said, highlight that in the beginning, but I think this specific area since it involves an oversight body, and since genetic counseling is a specific profession, I think here it would be better to expand it to genetic and genomic counseling.

MS. GOODWIN: Do you think we need, just for consistency of terminology, do you think we need to change the term throughout the report, though? Or just in this particular recommendation?

MS. MASNY: No. No, just in this particular area. Especially if we're asking the Secretary to assign a body who would be overseeing this, I think it would be critical at this point to make sure that it's as expansive, and is not just the genetic counseling profession.

MS. CARR: What if you said "including genomic?" Then it would be you're trying to remind at that point that that key point, make a reminder that we're encompassing both.

MS. MASNY: Well, I think if you say including genomic, then it means that there is genetic counseling for genomic conditions. I think that as the field evolves, it will be other health professionals who will be providing the genomic counseling, not just genetic counselors. So I don't think we should put it in a way, phrase it, that it would just include genomic.

MS. BERRY: I don't want to get too bogged down in editing this at all. Do you feel strongly that --

MS. MASNY: I think just in the number one section there, the first bullet, identify an appropriate entity to determine which health professionals are qualified to provide genetic/genomic counseling services.

Because I think, again, there is a specific connotation to what genetic counseling means, and I think that's where we could get into problems with this.

MS. GOODWIN: I don't have the specific language in front of me for the definition that is used, but when the term is defined, it is meant to capture I think how you are defining genomic counseling,

and it does point out that these services are provided not just by genetic counselors, but by a broad range of providers.

So I think at least the definition as we have it set out in the beginning of the report does include single gene counseling, and also how you've described genomic counseling as well as that it is provided by a breadth of health professionals.

MS. MASNY: Would we be able then to just put, you know how sometimes you say see Table 1, or see that page with the definition again so that people would know that it refers back to that?

MS. GOODWIN: We could do that, certainly.

MS. MASNY: All right. Thank you.

MS. BERRY: Emily?

DR. WINN-DEEN: So I vote to approve it.

MS. BERRY: Julio?

DR. LICINIO: I vote yes.

MS. BERRY: Sylvia?

MS. AU: I approve it. I just had one point of clarification on 7A. When you say you took out directly billed payers for their services and put directly bill for their services, that is a little confusing because you can directly bill anybody, the family, the doctor, the hospital, you know, because I think we had put payers because it was specifically third party payers that we were looking at, wasn't it? I can't remember. 7A.

You are deleting the word "payers," and you are just putting "directly bill" for their services. It's like, who? I don't know if that's a little confusing.

MS. BERRY: Does anybody feel strongly about that? I think it's implied, the word "payers" is implied, even if it's not in there. It you're going to bill someone, you're billing them with the

expectation that they'll be paying the bill, hopefully. Any other thoughts on that?

DR. LICINIO: I haven't thought about it, but it is a good point. I mean, are we talking about billing the person directly, or merely third party payers? Or anybody?

MS. BERRY: Okay.

MS. AU: I mean, that does make a big difference in the reimbursement world.

DR. LICINIO: Yes, because anybody can go and bill a person directly, but the question is who will the third party payer pay to, you know? Only some people are credentialed to be paid.

MS. BERRY: Okay.

DR. LICINIO: So that's an issue.

MS. BERRY: All right. Let's add that in there. Is it going to change anybody's recommendation if we add that in there? Okay.

Joseph, we didn't get your vote. I'm sorry. You snuck in.

DR. TELFAIR: No, I approve.

MS. BERRY: Okay. All right. The committee approves the edited version of the recommendations for the coverage and reimbursement report. That report will be finalized and then transmitted in short order to the Secretary.

All right. The next order of business is really to proceed to today's agenda. The issue of genetic discrimination will be the first item of business. As you all know, those of you who have been following this committee's work, the issue of genetic discrimination, health insurance and employment has been really our top priority.

We have been closely monitoring federal legislative activities on the issue, and in May the committee sent Secretary Leavitt a compilation of public comments, a DVD of testimony that we heard last fall highlighting various public perspectives on the genetic discrimination issue, and a legal analysis of

the adequacy of current law.

These three items were also disseminated to the public through the committee's website. This morning we will hear an update on the status of federal genetic nondiscrimination legislation, and a report on public attitudes about the privacy and misuse of genetic information.

Sharon Terry is here today representing the Coalition for Genetic Fairness. As many of you know, she's also President and CEO of the Genetic Alliance, an international coalition -- oh, Sharon is not here today. Frank? Where is he? There he is. Frank Swain. He's already seated at the table. Frank will be standing in for Sharon with the Genetic Alliance.

MR. SWAIN: I don't have slides.

MS. BERRY: You don't have slides? Okay. Well, thank you very much, Frank, for joining us this morning and for standing in. We appreciate it. With that, we will turn to you.

I just ask members of the committee that unless there are specific points of clarification, let's hold our questions until after all the presenters have completed their presentations.

MR. SWAIN: Well, thank you very much. It's a real pleasure to appear officially before the committee. I've been able to monitor the last two meetings here at least, and am very aware of the committee's strong interest in this legislation.

I told Sharon, who emailed me about 11:48 the night before last and said could I do this for her, for some odd reason, I was looking at my Blackberry when that came in, so that says something probably odd about both of us. I said certainly, but I would be a pale imitation for those of you who know Sharon. She's a whirling dervish in this issue area, on a broad set of issues. It's a real honor to represent her and her coalition.

We will do Q&A in a little bit under the schedule. Anything that I mention, I'd be happy to try to respond to to the extent possible and appropriate.

Let me review the bidding briefly. Our law firm has been working with the coalition for about eight months now to give additional push to this legislation, which as was mentioned, has been a concept around for quite awhile.

The legislation that has been introduced in the House of Representatives is H.R. 1227. It is a bill that essentially has two titles. One of the titles would prohibit the misuse, that is the negative use of predictive genetic information about an individual in the employment context. The second title would do the same, prohibiting the negative use of predictive genetic information about an employee in the health insurance context.

This legislation, as introduced, is identical to legislation that was passed by the U.S. Senate in February, 97 to nothing. Unfortunately, the House is not about to pass it to 97 or 497 to nothing. There is significantly more controversy about the legislation in the House of Representatives this year, as there has been in each of the past Congresses for the last two or three sessions of Congress.

The two titles of the bill are assigned to two different committees. The employment title is assigned to the committee that has jurisdiction over labor matters, the health insurance title is assigned to the committee that has jurisdiction over health insurance matters and other insurance matters.

Additionally, some parts of the bill must be reviewed by the Ways and Means Committee, because it affects indirectly at least the Medicare program, and the Ways and Means Committee has jurisdiction over the Medicare Program. So we have a procedurally challenging project to get everybody moving forward hopefully at the same time, and in the same direction.

As I'm sitting here this morning, the bill has 150 cosponsors. The primary sponsor is Congresswoman Judy Biggert from suburban Chicago, and a more energetic and committed sponsor we could not find if we had perfect hindsight. She is marvelous. She is aggressively bringing in many of her fellow Republicans who she corners on the floor of the House and essentially twists their arm into signing

onto her bill.

She knows what she's talking about. She is a lawyer who has practiced employment law. She also is a member of the House Science Committee, and has been significantly involved in the discussion at the Science Committee reviewing the progress of the Human Genome Project and the funding that went into that, and continues to go into that project. She speaks very directly and very sincerely when she says it is really silly for us to have invested hundreds of millions and billions of dollars of taxpayer money that we have in unraveling the human genome, and have everyone afraid to look at it.

I won't preach to the choir about the need for this bill. I will try to discuss some of the issues that we've come up against. First of all, the 150 cosponsors is significant. I recall back in March, the bill had not yet been introduced. Indeed we were on the cuspid of having it introduced, and you folks were pressing us fairly hard about what is going on, and we really couldn't say anything because it is really not appropriate to do it until the member sponsors it. But it was introduced I believe on March 10th with 40 cosponsors.

When I attended your June meeting, it had about 80 cosponsors. Today it has about 150. On that basis, in about two more meetings, we should have the entire House cosponsoring it. But unfortunately it probably won't just run geometrically from here on out.

The issues that we are dealing with are primarily issues raised by the business community, some parts of whom have significant apprehension that the bill will make it unduly easy to challenge routine workplace decisions using the hook of genetic nondiscrimination. Or to be more blunt, if negative action is taken against an employee, an employee is feeling litigious, he or she may say, you're discriminating against me on the basis of gender, ethnicity, religion, or age, and now add genetics into the alphabet soup of claims against the employer.

That is the fear of some. Not all by any means, but of some in the employer community.

That is one of the issues that we are trying to work through to make sure that the bill is clearly written, that it clearly does what it is supposed to do, and does no more than that, that the bill is not some vehicle to bootstrap a solution to every perceived issue with our health delivery system.

There are those who say well, if this bill is passed and everybody is found to have some sort of genetic defect, this will somehow inevitably march us towards national health care. I don't understand that logic myself, but we hear that with some regularity.

We hear some other issues that are more mundane and more solvable. For example, there are a significant number of individuals in this country who do receive insurance through single life policies. That is, they are not members of groups. They buy their health insurance in the individual market.

In the individual market, there is clearly medical underwriting. You can't be in the individual insurance market without having medical underwriting. Part of medical underwriting in most cases, and I think this committee is well on record, as are many groups, in favor of family histories. You go to a doctor, and if the doctor is a good doctor, that doctor spends some time taking a family history.

Somebody says well, the family history is in effect a genetic history. So does that mean that if we use the family history in some decision, that that is therefore a violation of H.R. 1227? Well, we are saying clearly not. We want to promote family history.

Well, what's the difference between saying that somebody had several siblings with cystic fibrosis and having a genetic test that says that the cystic fibrosis gene is present? Well, those are the kinds of issues that we're trying to work out at this point. They are in my view, legitimate issues, and in my view, we're well on our way to working many of the important issues out.

At some point obviously we'll just draw a line in the sand and ask our sponsors to go out and get the legislation up and scheduled.

We are involved in informal but I think useful discussions with the U.S. Chamber of

Commerce, the National Manufacturers Association, and some other groups that have had some traditional concerns about this legislation. It would be inappropriate for me and premature even if it were appropriate for me to say what the Chamber and the NAM are eventually going to do. I don't know what they're going to do, but it is at least a positive that they have agreed to sit down and talk with us and see if something can't be worked out on issues where there seems to be disagreement.

Finally, I might add that it is very important, the work that this advisory committee does candidly in urging the Secretary to take the positions that they must take. The administration thankfully is very strongly on record in favor of this legislation. But we need active advocacy at every level within the administration, within the scientific community, and within the business community.

Perhaps I'm being more candid than I should. One of the disappointments is that the business community, and in particular the biotechnology and the pharmaceutical community, have not really stepped up to the plate on this legislation, although many participants in that community would be very directly and possibly impacted if we could remove the apprehension that has been clearly documented in the public at large over having genetic tests and having genetic tests used in product and scientific development.

Finally, I might add there has been a very interesting case, situation, involving a professional basketball player, an NBA basketball player, who was with the Chicago Bulls. I'm not an expert by any means on the physiology of his condition or his alleged condition, but the Bulls said that they wanted him to have a genetic test because there was a concern that he had some sort of coronary condition that might result in his dropping dead on the basketball court.

He refused to have that genetic test. He has since been traded to the New York Knicks where presumably he will play basketball without a genetic test, or without at least publicly talking about whether he's had one or not.

The interesting thing, and this is a classic case of hard cases probably make bad law, and

I'd be happy to discuss it further in Q&A if you're interested, because there are a lot of individual situations there. They are not clearly generalizable to the public at large.

But it has galvanized attention, at least in the midwest, on this issue. The Chicago Tribune has come out with an editorial endorsing this legislation, and has had a fairly interesting series of articles about this as a case study in what may happen and what employers might do in the future.

I'm not sure how far you can push it, but it is a vivid reminder of the sorts of issues that are out there, and the reason that we need a federal law to clearly set out for individuals that live in every state, not just in the 33 states that have state laws on the book, what the rights and responsibilities of employers, employees, and insurance companies are in this very important area.

With that, I will close my PowerPointless presentation.

MS. BERRY: Thank you very much, Frank.

Don't go away, because we'll have some questions and we'll enjoy hearing your views on the case that you just raised, and other matters.

Is Christy here? Christy White is principal and co-founder of Cogent Research Corporation, a strategic research marketing firm, and she will be presenting a report on Cogent's research findings on public attitudes about the privacy and misuse of genetic information, the role of the government in protecting that information, and government access to genetic information. A copy of Ms. White's biosketch can be found in the briefing book.

MS. WHITE: Thank you for having us here today. We're honored to be able to speak to you about this topic that we believe is very important, and in fact have been tracking for a few years now, and plan to do so into the future.

Cogent is a market research firm. We're in Cambridge, Mass. We've been around for around 10 years. The majority of the work that we do is proprietary in nature. We do a lot of work with

industry, and a lot of work with the government as well. We saw this as an important issue to start tracking on behalf of both populations.

The objective of the research was to provide a very comprehensive and actionable assessment of where American views were at that point in time, a snapshot toward genomics so that we could help inform industry strategy and policy development.

The study itself looks at four main areas. Awareness, favorability, and interest towards genomics. So we start out very basically trying to understand what they know about genes in general, and the relationship between genes and health. Also what they know about genomics in particular, what they think about it on a general level for the population as a whole, and how interested they are on a personal level for themselves.

The study also looks at the specific catalysts and barriers to adoption and usage, trying to understand what are the perceived benefits and drawbacks, what are their fears and hopes for genomics for them, and for the public as a whole.

We also look at lot at preferences for delivery. I won't spend any time on that today. That's my industry speech. But we look a lot, and if anyone is interested in that, we do have some very interesting data on what will maximize consumer interest in terms of how they want to get the information, who they want to be involved in the decision whether or not to have a test or not, how they want the information delivered to them, and how they want the information stored. I will touch on that to the extent that it relates to the topic here today.

Lastly, we look at messaging and communication. So using some of the information that we know from qualitative research, I'm going to be speaking to the quant study here. What are some of the potential messages and things that we might say to consumers to alleviate some of the fears that they have, or address some of the concerns.

The methodology for this study was a web-based study. We looked at U.S. adults, 18 plus. This profile of the sample is representative of the U.S. population on key socioeconomic variables, ethnicity, region, and gender. These are back to the 2003 projections, that's the data that we use for comparisons there.

We conducted the data last January, in the middle of January. We're actually getting ready to run the study again, we'll probably run it toward the end of January this year for our third year. This survey, as I mentioned earlier, the majority of what we do is proprietary in nature. This study was ours, so we had full control over it. We got a little out of control, we have 205 questions. There is a lot to know, explore, and look into on this topic.

We talked to a total of 1,000 consumers, which gives us a sampling of plus or minus three at the mid-range. We looked at a wide variety, a good chunk of those questions, probably around 40 of them are demographic questions. We really wanted to be able to tease out what are some of the differences by some of these different key demographics. We also conducted a robust psychographic segmentation model. So if we clump people together by their belief systems, as opposed to a demographic like age, can we understand or tease out some differences in the population in terms of what's happening.

There are a few things that we're going to do differently next year when we run this. There are a couple of areas we're going to look into, and this is based upon some meetings I've had both with government and industry. We're going to delve more deeply into people's awareness and usage of Internet-based products. I know this is something the CDC is very interested in in particular.

We'll also be looking more completely at workplace discrimination. We do touch on that here. Our focus was mostly on insurance and government this past year, but we will be looking more closely at workplace discrimination.

Also awareness of the current legislation and protections that are in place. We want to

understand, you know, do people know what protections there are, what do they think of those protections, and what would their hopes be for where those protections might go? What would actually have an impact on that?

So that data, as I imagine, would be of interest to this committee, would be available I'm guessing early February of next year. We'd be happy to come back and talk about that.

So I'm going to walk through just a few key findings from the study, probably around 40 of the 200 questions. So it will give you a good picture, but clearly there's a lot more here.

The first basic thing we want to know is are consumers even aware of the issue. We asked them how much they have heard or read about using individual genetic information to understand and optimize health. You can see that awareness is very broad, three-quarters of Americans saying that they have heard at least something about this issue.

When we delve a little bit deeper into it, we understand that it is really not a very sophisticated understanding. Only 4 percent of Americans are telling us that they have heard a lot, one-third of those who say they have heard something can't recall any specific details. Of those who can recall those details, they are mostly telling us that they understand there is a relationship between genes and health, and not specifically how they can use that genetic information to potentially alter or improve their health.

There are a few, however, that are getting at least to some extent, a more sophisticated understanding of what's happening. They tell us things like genes can be manipulated from a health benefit, they can lead to early diagnosis and detection, they can help find cures for diseases, and then of course can be used in the prenatal stage. So there are some consumers that are at that more sophisticated level of understanding.

We do know from qualitative research that this is classic, this is what they'll say back to us. It is very easy to get them to make the leap. So although everyone is aware and they're just aware in

general about the relationship, it is not difficult to get them to make that leap almost on their own of how they could start harnessing the power of that information for themselves.

When we look specifically at interest around prescription drugs, making informed choices about prescription drugs, awareness drops to 43 percent. So we've got 75 percent getting that specific level of just the general level of understanding, but 43 percent with prescription drugs. That is still actually not a very low number.

So what are their general attitudes? Their attitudes are highly favorable. You can see in general when we asked them, "In general, how favorable are you toward the idea of using genetic information to understand and optimize health?" You see more than half of Americans are saying that they're favorable.

This is actually quite a high number. We might expect to see a bell curve here with the majority of people being in that sort of middle level, particularly since they don't fully understand it yet. But we see that there are a lot of people that are very excited, and they see a lot of promise in genomics in general.

They are also as excited about it on a personal level. So when we asked them, "How interested would you be in using your genetic information for the purpose of understanding and optimizing your health?," you can see that that interest is still quite high.

So how does that play out for personalized medicine in particular? Fifty-eight percent of the U.S. population, or adults, are saying that they're favorable towards using their individual information to make informed choices about prescription drugs, and 51 percent are interested in using that information for themselves personally.

What we did at this point in the survey was we delved more deeply, so we're trying now to give them this understanding of how they can use the information. There are specific ways in which they

might use their genetic information when it comes to personalized medicine or prescription medicine in particular.

We looked at three areas. Efficacy, so which drugs would be most effective in your body, safety, whether they would have an adverse reaction to the drug, and prevention, whether they would take the drug preventively.

Probably not surprisingly, safety -- these are all very high and quite close, but safety is clearly the one that they're most interested in in terms of the usage. But very close behind that comes efficacy, and not surprisingly, the third would be preventative or proactive usage of prescription medication.

So I think what these slides do is they present a picture for us that consumers, they're ready. They're interested in this, they can easily be brought along. They are interested anyway, and they can easily be brought around to understanding how they can use it. When you express it to them, they say yes, I'm interested in doing that on a personal level. What we'll look at now is the how, what it is that needs to be in place for them to actually do this.

So from a variety of data, both qualitative and quantitative, and a variety of different types of questions, we see that interest is solution-driven. By that, what we mean is that they are interested in reducing their risk of specific diseases. We asked other questions like would you want to do this just to get a genetic profile for yourself and your family, and for posterity sake, would they be interested in doing it for health benefits such as sleep, things like that.

Really where the interest is greatest, and the interest is great across the board, and that's one of the things I should have mentioned earlier. There is not one key demographic group where interest drops below 40 percent. So unlike other areas, or even when we're working with industry, we go and say these are the people to target. It's high income, it's this, it's that.

In this particular case, interest is so broad that there are opportunities for all Americans in

terms of products that could be created, and they are taking advantage of them. But in particular, they want to focus specifically on reducing diseases.

They also are most interested in finding out information if they are certain to experience that, and I know that may be something that's very hard to deliver on, but their concern is that they don't want information if they can't do anything about it. Again, they are still interested in that, but they're more interested if you can tell them they're certain to experience that.

And lastly, they want to know that there is some treatment. So tell me I'm at risk for this disease, I'm definitely going to get it, and tell me that there is something you can do for me.

There are three key things that we believe are critical to long term and continued acceptance of genomics. They relate to privacy concerns, emotional consequences, and moral issues. There is a very high correlation between these three variables and favorability and interest.

The privacy concerns are there at the bottom, because it is sort of the barrier that we have to get through to even be talking with them. It's a big concern for them, and it's something that we need to address and deal with. Right now they're on the fence about whether or not there is an issue, and we'll talk about that.

Ethics are at the top because I think they have the potential to topple this whole thing ultimately. We'll talk about that, too. So down at the bottom, I think what privacy can result in for Americans is limited usage of genomics. What the ethical issues can do to this is that there would be no usage of genomics.

We looked at privacy from three issues, as I mentioned earlier. Employers, government, and insurance, mostly focusing on insurance and government this time around. But from both qualitative and quantitative, these are the dominant issues that come into play when you ask them about things that might limit their usage of genomics.

So we'll start with the moral issues. What we're showing here are the top two boxes in the blue for agreement with a few statements, which I'll read to you. What we have done here is we have thrown in those people in the midpoint, the three on the five point scale. We're calling those the people who are the fence sitters.

So when you look at some of these statements that relate to ethics and moral issues in general, you can see that close to 50 percent of the public either agree with some of these statements, or they're on the fence. They have the potential to be swayed to agree with some of these arguments.

The first one, "Some of the recent advancements surrounding the use of genetic testing make me uncomfortable from a moral standpoint." So about one-fourth agree with that, and 55 percent total, we include the fence sitters.

"Meddling with our genes and DNA is trying to play God. Scientists, researchers, and doctors should stay out of it altogether." A little bit less agreement, but still we're getting close to 50 percent when we include the fence sitters.

Lastly, "Genetic testing should be stopped, because it will ultimately lead to cloning or altering human genes." Fifteen percent agree, 45 percent fence sitters.

I think that there are lots of examples of scientific advances that have either been stopped, or at least the public hasn't been able to benefit from them fully because of moral arguments that have been made. This, you can see that these are a minority of people, potentially a vocal minority, and potentially a large percentage of Americans that could be swayed one way or another.

Talking about that middle part of the pyramid now, the emotional costs. So this really relates to the fact that knowing my genetic profile is too great a responsibility, it impacts myself, my spouse, and ultimately my children's lives. So close to one-fourth of Americans are saying they agree with that. Slightly more are saying that it would be depressing to know I was going to get a disease, or too depressing

to know I was going to get a disease, particularly if there is nothing I can do about it.

So this is not as big of an issue as privacy, which we'll now move onto, but certainly it is something that needs to be addressed.

Privacy. So 68 percent of Americans are telling us they're concerned, it's a 4 and a 5 on a 5-point scale, about how their personal genetic information would be stored, and who would have access to that information. One-third of all Americans, not just out of that subset, but one-third of all Americans are telling us that their concern would prevent them from having a genetic test. So it's not at a great level yet, but could potentially be an issue.

So trying to understand a little bit about why they are concerned, of course everything we've talked about already, but specifically here, one-third of Americans are saying that they consider the results provided by DNA testing to be more sensitive than results provided by other tests, so there is an understanding there that that information is potentially more dangerous for them specifically if it were to be misused.

Also, about half of Americans say that they are torn on the use of genetics. That gets back to that point I made about the ethics with the fence sitters. But here what they're talking about is the potential benefits are incredible, but the potential for misuse is considerable.

Misuse predominantly means that people are worried, half of the Americans are saying worried that their DNA sample may be used for tests other than the ones that I have authorized. We see this in qualitative all the time when you ask them about their concerns.

This issue that, well, what is going to happen to my DNA, who is going to have access to it, who is going to make sure that no one has access to it? So let's talk about misuse.

Not that this is probably a huge surprise, but there is a lot of concern about insurance companies in particular here. We had put in a few inflammatory statements with the goal of really trying to

tease out who are those people who are concerned about insurance. As you can see, even with a statement like, "Insurance companies will do everything possible to use my genetic information to deny health coverage," 68 percent of Americans agree with that statement.

"Insurance companies will use the information to deny coverage for drugs people need if the genetic profile indicates a low chance of responding." And 60 percent say that their level of interest would decrease if the information became part of their medical record, and was therefore obtainable by insurance companies.

However, they do want insurance companies to pay for these tests. Fifty-three percent say that their interest level would be decreased if the insurance company would not cover the costs of genetic tests.

The role of the government in privacy, as I mentioned, we're going to put in some more questions about this the next time we run this. At this point, what we do know is that Americans do want the government to protect their privacy.

Sixty-four percent say that their interest would be increased on a personal level if they were assured by law that no one could access their DNA information without their consent. What we want to do next time is understand, well, do they think there are protections in place and they don't think they're adequate, or do they not understand there are any protections in place, and what do they think of the current protections that are in place? We'd be happy to work with someone on this committee if they want to look at those specific questions before we field them.

"The government should establish specific laws and regulations to protect the privacy of genetic information." Seventy-one percent are agreeing with that. The majority were on the fence otherwise. There was not a lot of people not agreeing with that.

Similar to what we saw with insurance companies, not trusting them but wanting them to

pay for it, we see a similar dynamic here. They want the government to protect their privacy, but they don't want them to have access to their information. Only 24 percent agree the government should create a national database of DNA information for the future health of all Americans, and only 1 percent when given a multiple choice that included a variety of different options selected the government as a place -- who beside you should receive a copy of the results of your genetic test? So only 1 percent of Americans thought that the government should have a copy of that.

These are some of the key learnings that we took away from the research, and some of these frankly have more to do with industry, but I think government certainly can get involved in some of these important issues.

First of all, we believe that there needs to be an effort to deepen American's understanding of genomics. We know there is a positive correlation between awareness and interest. So whatever they're reading so far has been positive, and it's leading them to be interested in this.
I think we know that when we draw a connection to how they can actually use it in their lives, they continue to be interested. So I think there's a need to deepen their understanding of how they can use genomics.

There needs to be a focus on diseases where solutions exist, because to my point earlier, if we're telling people about diseases that they're likely to get and there's no solution for it, we're just unnecessarily upsetting them.

Advocating for privacy protections with limited involvement. So on both levels, protections, government-related and insurance-related with limited involvement from those parties in terms of access to information, and addressing the moral concerns or framing the moral issues in a way that can help people understand how this can benefit them in the long term, and what the ethical benefits are to genomics.

And that is it.

MS. BERRY: Thank you very much.

Let's throw it over to questions from members of the committee. Julio, and then Sylvia.

DR. LICINIO: I had a question about the legislation that's in Congress right now. Is it the kind of protection that let's say when you go to the, just as an example, I went to the clinic last week for my own medical need. You have to sign so many forms waiving every kind of, you know, as far as giving access to your records for the insurance company. Like four or five forms, you can hardly understand them.

A lot of people look at very fine print, and you know, do I really want to do this or not? Is this the kind of law, let's say if it's passed, could it just be in the fine print somewhere that you waive your right to genetic privacy for insurance purposes for that purpose? So even though there is an overall like, you know, an overarching principle, it is something that could be waived for third party reimbursement.

MR. SWAIN: I think the same people that design the home residence sale closing forms package are now working in the insurance and health insurance industry. It is not quite that thick yet, but it is getting there.

The quick answer to your question is that individuals have broad authority to waive protections. Health insurance companies have many reasons to, if you seek a health insurance company's reimbursement, they, under their insurance contract, may demand to know details of why that reimbursement is being sought. So that's part of what health insurance is all about, to decide whether treatment is appropriate, unnecessary, or excessive, whatever the case may be.

So typically that's the basic waiver. The doctor is not supposed to share the information that they have about your health condition with anyone else unless you allow them to. So you waive it and say you can send it to my insurance company that's going to pay for this.

I don't see anything in this legislation that will stop or alter that. The health insurance company will still be allowed to have that information. Actually, that's an important question that I'm glad

you asked. Everybody that is in the normal flow of genetic information would still be allowed to have that information. It's not the having of the information that's the problem, it's the misuse of it.

If the health insurance company turns around and increases your premium because something in the genetic information suggests that in five years, you may acquire a particular health condition that you don't have now, that would be a misuse under the bill. But for them to have the information would not be misuse under the bill.

MS. BERRY: Sylvia?

MS. AU: My question is for Christy, and a comment. Could you tell me a little bit more about how you got the broad range of demographics for the study that was Internet-based? And then my plea to you is in the presentation, you kept saying Americans, Americans, and it's only 1,010 people. I think it is survey participants attitudes more than Americans.

MS. WHITE: Well, the data is projectable. The data is projectable to the U.S. population with a sampling error of plus or minus three. So when we say that, we're saying Americans, but to your point, yes, within the sampling error that allows. That's the worst case scenario for sampling error, because there's a lot of agreement to a lot of these questions. In most cases we're looking at a sampling error projectable to the U.S. population. I shouldn't even say Americans, actually, but to the U.S. population of at worst case, it is plus or minus three.

In terms of how we collected the data, there are a variety of Internet panels that exist, web-based panels that exist. For this study, we used Greenfield Online. Probably a lot of you have heard of them. They are one of the largest panel houses.

Their panel is somewhere in excess of 7 million Americans at this point. They generate their sample through a variety of means, intercepting people off the web. They do a lot of in-home calling into the homes. We know that the U.S. at this point, in excess of 80 percent of the U.S. population has

access to the web, and we are very cognizant of the fact that there are specific populations that are not on the web at this point. I shouldn't say on the web, but underrepresented on the web.

Particularly they are people over the age of 75, Hispanics, and people with less than a high school education. So what we do is we oversample for those populations when we go out, and similar to what we would do with a phone survey, mail survey, or any methodology, we look at the distribution of responses to the U.S. population on key variables, the census data, and we weigh the data accordingly.

Typically with every web survey that's done, you have to wait for those populations, because they're very difficult to get on the web. Certainly there is a chunk of people that are not on the web in the U.S., and they are not represented in the study.

We find that there are as many if not more challenges in conducting phone-based research these days. What happens with phone-based research is you are underrepresenting the high income, high education population that are savvy enough or quick enough to hang up on your predictive dialers, or just tell you that they're on the do not call list. We don't get into an argument with them to tell them that that doesn't really include us. We have to say thank you very much, we are sorry we bothered you, and hang up.

So there are challenges with every methodology today. About one-third of all the research we do is web-based. We've been doing it for ten years. We were one of the first companies doing it, and we are very rigorous probably to the upset of all of the web panels in terms of how they pull the sample, and what we get back in terms of results.

But your point is well taken.

MS. BERRY: Kevin?

DR. FITZGERALD: I have a couple of questions, if I can do one for each. Thank you.

First of all, Ms. White, I was very appreciative, at the end you were talking about in a sense how you ask the question can certainly lead your group one way or the other.

So sort of to make it even more generic, what do you think would happen to your numbers if you substituted the word "nanotechnology" instead of genetics?

MS. WHITE: Well, we always try to do qualitative research before our quantitative so we understand which terminology we can use and not use. For example, "gene expression" was something we wanted to talk about initially, and from our qualitative research, it was clear that consumers could not understand that terminology.

So we through qualitative try to understand what are the terms we can use and not use. I mean, we would never use a term like nanotechnology. In fact, we try to keep all of our surveys at a 6th grade reading level, to the extent possible, because that way we can ensure that all the survey respondents are in fact understanding the question.

We also not only talk to them beforehand to understand what we can say, but we pretest the survey instruments. So once the actual questions are written, we have a small number of Americans of the U.S. population go through the survey as if they are a respondent, and then when they're done, we walk through and say every question, what did you think we were asking you here, what did it mean, was anything confusing, hard to understand? We added the survey accordingly from that.

DR. FITZGERALD: Okay. Thank you. Then Mr. Swain, one thing you mentioned, I think it's going to be very interesting to see how this shakes out, this idea of family history versus genetic information.

In a sense, one could use either to sort of get a percentage risk one could say in predicting the future health of an particular individual, family, group, or something like that. I'd like to hear more about how this difference is going to attempt to be clarified in the law.

MR. SWAIN: I guess I'm tempted to say I'd be happy to further comment if I can have your assistance as we mediate this issue. It is obviously semantics, it is conceptual. I just have to go back to

our starting point, which has been drummed into me by Sharon Terry, which is that this legislation is intended to remove the popular apprehension about receiving or undergoing genetic testing.

It is not intended to change anything else that's good or bad about our health care system. It is not intended to prohibit or curtail the ability of physicians to take family histories. If some lawyer got in there and read the bill and said this would prevent taking or using family history, then it's our obligation to try to work around that.

We aren't at the end of that process yet, but conceptually, that's where we're starting.

DR. FITZGERALD: Thank you.

MS. BERRY: Agnes?

MS. MASNY: I'd like to thank you, Mr. Swain, for your presentation. We really appreciated the work of the coalition to help move this legislation along. We would hope that you continue in your efforts in back of Ms. Terry.

Ms. White, I just wanted to also say that we're very happy to see that you're reporting on numbers regarding the public's concern about both the privacy issues and the misuse of genetic information. I think this is one thing that the committee has long been asking for to get further and further numbers regarding this issue. So I just have a question based on that then for the committee, our committee itself, is whether we could make use of the numbers, the summary of the presentation today, to add as an addendum to what we've already sent to the Secretary, if that would be okay to do.

I think it continues to add to the momentum of the need for this type of legislation.

MS. WHITE: We'd be honored if you did that.

MS. BERRY: Suzanne and Julio.

DR. FEETHAM: A question for Ms. White. You were very deliberative obviously and scientific in your sampling.

My question to you is are you designing this as you go into the third year that you can be looking at trend data?

MS. WHITE: We did actually trend the data to last year. There were not a lot of changes. Actually I was a little disheartened to see that awareness had not increased over the past year.

We did go back and do a literature search to see if there had been an increase, because it seems that way to me. You know, when you buy a red car, it seems like everyone drives red cars. So I thought gee, every time I turn around I'm hearing a story about this. I was surprised that awareness did not increase. But in fact the literature search showed that there was not actually an increase in the number of stories.

But everything pretty much stayed flat from last year, and we will definitely trend that data again. Where there are differences, we'll start to report on them, and hopefully we'll see some of those differences soon.

MS. BERRY: Julio?

DR. LICINIO: I had a question for Mr. Swain, just a clarification. This bill passed overwhelming in the Senate last season, right? And the issue has been the House. Am I understanding that the biggest issue is really the business community's fear that if you try to terminate someone's employment, it is going to be they can kind of turn back and say they are discriminating against me because of my genetic background?

MR. SWAIN: That's correct.

DR. LICINIO: I hear the words, but I don't understand how that would actually happen in practice. I mean, what genetic background could someone discriminate against? I mean, you say I have this particular, you know, gene, and you are firing me because of that? It's so illogical that I can't follow.

MR. SWAIN: Well, many are in your situation. The business community is a bit

illogical, because on the one hand they say of course we don't discriminate, we don't, and we would never discriminate on the basis of genetic information. But on the other hand, we're fearful of this law that would say that we could not discriminate.

Putting aside that logical inconsistency, the discrimination to the extent that it is there or it is perceived to be there is less likely to be someone is going to be fired because, or lose their job, but someone may not be hired because breast cancer, a genetic marker is in their medical file for breast cancer.

So they might not be hired. Why would they not be hired? Probably because the employer would be concerned that it will cost that insurance plan a lot of money when that person gets ill. I hate to be so direct about it, but generally speaking because employers don't like people who have a certain kind of gene, they are really probably looking at it from a dollars and cents standpoint. They don't want to hire somebody that they think is going to cost the health insurance plan a lot of money in some future years.

Now, I say "they." In fact, I don't think most employers operate that way. There are some that do, unfortunately, and I suspect, I have represented employers for a long time in various contexts, and there are certainly outliers. But there is a concern about that, that even if I'm a good employer, for every 1,000 employment decisions I make, I know that 100 of those are going to sue me. Out of those 100, if 10 of those can add genetic discrimination, it's going to cost me a lot more time and effort to fight that off, even though I'm a good employer and I only make decisions on the merits. So it's that balance that we're trying to strike.

MS. BERRY: Joseph?

DR. TELFAIR: I want to thank both of you for the presentations. I appreciated that. My question is for Ms. White.

In the sort of next to last slide, you had a contrasting example there between, which is this, I see it sort of consistent on what subject you ask. Is that should the government work really hard to

protect your rights? The answer is yes.

Should the government be able to tell you what to do or whatever should be no. The question I have, because it's relevant to decisions we have to make in terms of recommendations is public engagement. Yesterday we had a lot of conversation of that, involving the public, advising us to make decisions in this way.

Did you have, or did you think of in your survey, maybe not some of the questions that are here, a willingness of individuals to work with the government in terms of making recommendations related to issues of privacy, issues of confidentiality, those sorts of things? Did you have any of that in your --

MS. WHITE: We didn't cover that issue specifically. I'm not sure. My inclination is to think that they would want to be involved, but you never know.

DR. TELFAIR: Well, I ask because that is a critical concern that this committee has. So thank you.

MS. WHITE: I mean, one of the things that we do on behalf of business all the time is create, we usually call them consumer groups or consultant groups, advisory groups that are made up of consumers. So if we're working with a pharmaceutical company and they are trying to figure out how to communicate something, you might get together a group of general consumers who are in their specific target audience and have them serve as an advisory board to the marketing team or the public communications team.

DR. TELFAIR: Well, ma'am, as you consider additional questions, could I sort of suggest that you may ask that? That may be something that's important.

MS. WHITE: Sure.

DR. TELFAIR: I would think this committee would be interested to see what the

direction is.

MS. WHITE: Absolutely.

DR. TELFAIR: Thank you.

MS. BERRY: I have a question for Mr. Swain. I was wondering if with the IBM announcement regarding its policy towards its employees and not using genetic information against them, have you seen any impact on your negotiations? Or is that rippling through the employer community or having no impact whatsoever? What is your view of that?

MR. SWAIN: Well, I think the IBM announcement, which was just a week or two ago, is really singular. It's obviously the right thing to do. I believe Sharon Terry served as an informal consultant at least to IBM working through some of the questions that came up internally.

It's a leadership move, and it is certainly our hope and Sharon's hope that many other U.S. companies and U.S. employers adopt and articulate similar policies. I don't really have any information to respond to your question because it's too recent.

I can tell you that our sponsors, particularly our republican sponsors in the Congress, are very happy about the IBM announcement, because it confirms what they are telling their business constituents, that it's really in your best interest to go ahead and support this bill.

I think it is going to have an influence, I think it is having an influence. It's a little too early for me to gauge what the level of it is.

MS. BERRY: Sherrie?

DR. HANS: My comment is actually a request for Ms. White. You indicated at the beginning of your talk that you do have data on the preference for delivery method in who is involved in returning genetic data and information.

Would it be possible for you to share that information with the committee and a couple of

top line slides that you have on that? I think it's particularly pertinent to the conversations we had yesterday about large population studies, and if and how such information should be returned to the participants if information is found.

MS. WHITE: Yes, we do have information on that. In particular, I think questions about how involved the physician would be in the decision or who influences would be, what level of influence different organizations would have on their adoption. For example, the government, pharmaceutical companies, health associations, we have a lot of data on that as well, which we're certainly happy to share.

We're also, and I don't know if I mentioned this, but we're also getting ready to launch the first physician-based study, which will be a complement to this research, which will look at physicians, both general practitioners and specific specialties, very similar, although you might not think it would be on the face of it, but what is their awareness, what are their perceptions, what are the catalysts and barriers to their adoption.

We would get of course more with them into usage, and then also looking at issues of how they would best like to have this delivered so that it's easier for them. We may remove some of the cost issues that are there.

So we'll also be starting, that study is going to be launched early next year as well, so we'll have some data there, too.

MS. BERRY: Thank you both very much for coming today and sharing your perspectives and your comments. I hope you don't mind, I'm sure many of us will want to follow up with you. We'll have additional questions and thoughts, and we'll enjoy working with you in the future.

MS. WHITE: Thank you.

MS. BERRY: With that, it's time to turn to our pharmacogenomics session. Emily Winn-Deen, chair of our Pharmacogenetics task force, will lead that session for us. She will provide an

overview of what will be discussed, and a review of the task force's work since our June meeting.

Emily?

DR. WINN-DEEN: So what I wanted to do to open this session today on pharmacogenomics is to just give you a quick overview of what the session is going to be and what the task force has been doing since we last met as a committee.

We have a very broad representation of committee members, as well as ex officios on the task force. I'm not going to read everybody's name here, because it's just too long to list, but I want to say that most of these people have been very active participants, and that we really have appreciated all of the viewpoints and the inputs that we've received.

Today's session is designed to continue the fact finding on some of the issues that we identified at the June meeting, and then to proceed with our work plan in terms of trying to develop a recommendation on what this committee should or shouldn't do in regards to this subject.

So in the June meeting, we identified a number of key issues, and those are summarized in your briefing books, so I hope everybody had a chance to just quickly review that. We also identified some areas where we felt we still had some gaps in our factual knowledge where we wanted to get a little bit more education and input.

In the R&D area, there were several areas we wanted to get some more input on, particularly on the drug diagnostic co-development. This is both happening on the industry side as well as the FDA side, and we'll hear a little bit about the FDA side today, as well as some of the pharma perspective, how the whole concept of pharmacogenomics is impacting the way research is done, the way evidence is collected on effectiveness and safety.

There are issues particularly on existing drugs of how one might fund pharmacogenomic studies, and who should be the right funding source for that. And then sort of a topic that's just out there

waiting for us to decide how we want to address it is to what extent does genetics segmenting of a disease or response to a drug lead to some kind of orphan disease status or orphan drug status potentially.

In the infrastructure area, we'll hear a little bit from FDA about their attempts to create some kind of data standards for pharmacogenomic data, at least as it comes into the FDA. There has been a lot of very active work done in consultation with the pharmaceutical industry to come together on kinds of data and how it should be submitted. We'll hear a little bit about progress and regulation, and also a little bit of feedback on how the first pass at trying to implement this is going.

One of the key issues of course is it is all nice to have all this stuff going on at the R&D level, and cool new science kind of level, but our real goal is to integrate this into clinical practice. That raises several issues. We talked a lot yesterday about some of these issues. I don't know if I need to go through them again, but we definitely need to deal with the access and education issues.

The specifics of pharmacogenetics or pharmacogenomics lead to a need to develop some kind of standards for evidence and guidelines on how this data should be used in clinical practice, and inevitably when you get to some kind of a clinical practice guidance, you lead yourself down the road of if you're not following the guidance, what kind of liability does that leave for the physician?

There is also in this area, again, a large number of ELSI issues. I think they are really in several sort of big lumps. One of which is is there going to be some kind of stratification that happens, unintentional stratification that happens based on social economic status, or, you know, access to insurance, access to physicians, that will instead of improving health, will actually create more health disparities.

You, again, with all genetic tests, have the issue of informed consent. But in this case, for a test that is really only going to tell you about your response to the drug, does that informed consent need to be at the same level of both education and consent that you would if you had a, you know, very severe genetic disease that you were talking to someone about, and how do you deal with those sort of

nuances of levels of both education, as well as informed consent.

Of course anytime you're going to be doing genetic analysis on someone, you get into the whole issue, as we just heard, about patient concern about having their data in a medical record, and what that might lead to in terms of any disclosures which they feel would violate their privacy or confidentiality, or whether they might be discriminated against.

I think it's less likely you'd be discriminated against if you're a poor metabolizer for 2D6 and if you're likely to come down with Huntington's. But still, we have to make sure that we have these kind of protections in place.

The issue of race I think comes into play here, particularly because of the recent approval of BiDil. It is the first drug approved for just a subsegment of the population. The question I think arises whether we could do a better job of segmenting the population based on a real genetic marker as opposed to what I think right now is really more a surrogate marker, and how can we move that ahead. We don't want to do any unintended harms. We want to make sure that the psychosocial consequences are minimized.

Then sort of outside of that, we have the issue of patents and intellectual property. This becomes extremely important when you get into the pharmaceutical side where the pharma industry commits a lot of money to developing a drug, and pretty much feels that they can't make that commitment without some kind of intellectual property position.

So how do we deal with that in terms of that influence on access and availability of health care? So the task force had one intervening conference call since the last meeting. The goal of that call was to basically plan today's session.

We asked the staff as well to survey basically all the HHS agencies to identify what ongoing federal efforts are already in place related to pharmacogenomics, and a summary of that survey was also in the briefing books. Then we discussed how we would develop a framework for committee

recommendations. We didn't actually try and frame any recommendations at this point, but just sort of talked about the process.

So today we are going to have sort of a two part thing. Before the break, we're going to hear an update from FDA, both the diagnostic side and the pharma side, to understand a little bit about what is going on, what's new in the ever changing world of FDA. There has been a lot of developments I think since the last meeting.

We are going to take a pause in the pharmacogenetic session to do public comments, and then we'll come back with some presentations that address the economic and financial issues surrounding how this is implemented in both drug development, as well as clinical practice.

Then finally to finish the session with the talk by Wylie Burke on ELSI issues, and particularly on how drug responses in different ethnic groups, what are the ELSI issues surrounding that particular subsegment of the global scope of pharmacogenomics.

So in terms of the federal efforts, I think I mentioned this already, the task force requested a review, and the goal of that was to inform an analysis of basically are there places where there is the same test being done by multiple agencies so you have overlap, or are there areas that we have identified as important for HHS to be working on, but no agency appears to have sort of picked up the ball and run with it.

I think that was, again, designed to help us with our recommendation to HHS about how the HHS agencies can best participate in this field.

We have developed an outline of a comprehensive report. Basically this came from all of the things that we have discussed over the last couple of meetings as issues. We got very good feedback I think from the public, although the folks that have had a chance to look at the coverage and reimbursement report are feeling that it was useful to have both a sort of state of the state summary, what things are,

definitions, you know, the basics of the field, and it provided us with a framework to make some specific recommendations. So the task force at least at this point is thinking that we could do something similar in this area.

With that, I will close my opening remarks. I'd like to introduce our two speakers from FDA. I don't know who is up first here on the schedule.

DR. GUTMAN: I'm first.

DR. WINN-DEEN: So Steve Gutman, who we know and love from his many years of service to SACGT and this committee, is going to give us an update first on the diagnostic side of the pharmacogenomics pipeline.

DR. GUTMAN: Yes, good morning. Dr. Rudman and I are going to play team tag here. So I'll start and he'll finish.

I guess my remarks to a certain extent will both support and belie the notion that there's nothing new under the sun. FDA and my work in particular has brought to market in the last year the first two I think what you could characterize as pharmacogenomic tests. The first was approved in December of last year, and that is the Roche Amplichip, and the second was approved over the summer, that is a UGT 1A1.

There were common themes in the review process for both of those products. Those products were brought through as Class 2 medical devices under a new de novo classification that was created for metabolic enzymes. The de novo process is a process that provides FDA with increased flexibility when it encounters a new test of this type, a lack of clear predicates, it does require either low risk or some ability to mitigate risk.

FDA's assessment was actually somewhat parallel for both of these devices, in that what makes these products stand out as tests is their analytical strength and their clinical imperfections. Their

clinical imperfections being rather transparent.

Both of these submissions were preceded by changes in CDER drug labeling for at least a model product. In the case of the Roche, that model product was Strattera. In the case of UGT 1A1, the model product was Irinotecan. The labeling changes that were made on the model product were advisory or cautionary, not strong required labeling changes. So they were modest changes, but they were changes on which we were able to feel comfortable about anchoring the de novo clearance process.

In all honesty, we do understand that the clearance of both products based on those models is a little bit like the Titanic approach the iceberg, that we looked at the tip, and there may be a little bit more than meets the eye.

Certainly if there were specific claims and specific performance parameters that were to be generated on top of either of these assays, we would probably like to be revisited with more submissions. That would probably be okay for UGT 1A1 since it doesn't seem to be an infinite spectrum of possibilities.

That might be more problematic for the Roche Amplichip since about 20 percent of medications in the country theoretically could be impacted. We could have dosing decisions, perhaps even selection decisions driven by information generated by the Amplichip, and that would provide incredible job security if we were to go after 20 percent of U.S. medications.

The medications that were best credentialed probably now, but certainly at the time of clearance were the neuropsychiatric drugs, and certainly the use for toxicity seemed very straightforward.

But as Emily sort of alluded to, there are some outstanding education use and reimbursement issues that FDA did not resolve when it cleared these two products. We were good for our word, in that when we talked at SACGT about dealing with these new tests, we said we put these tests out trying to be as transparent as possible to let people know what we knew about the test, and to follow Elliott's admonition, to also be sure that we communicated what we didn't know about the test.

More globally, as Emily alluded to, there is a very novel from our work ethic point of view, a concept paper which represents a joint effort of the Center for Drugs, the Center for Biologics, and the Center for Devices on the co-development of diagnostics as they might relate to drugs.

It is a long document, maybe it's a little too long a document, but in my view, and I'm bias because I'm close to the document, it rather reasonably limns in a preliminary manner the scientific issues on the plate for analytical validation of this type of test, for clinical validation of this type of test, and for elucidating the clinical utility for this type of test.

It makes a very important point that when a diagnostic is used to select a drug, the two become inextricably intertwined, and that I think most people are cognizant of the fact that the diagnostic may drive the performance of the drug. I think a more arcane and missed point is that the performance of the drug may drive the performance of the diagnostic, because the response to the drug behaves for the diagnostic in the same way that prevalence behaves for diagnostic, and can radically change the prevalence of a response, and therefore can radically change the predictive value of a positive and negative result.

That is very parochial and arcane, but a very important point. It is hidden in Appendix C of this concept paper. Anyone who actually is interested in that should look at Appendix C, because we actually tried to make that simple.

The comments, and we did get wonderful comments, a wide range of comments, but probably the most powerful two comments were the comment that the document, which was certainly not intended to be prescriptive and suggest that one size fits all, but was clearly aimed at an idealized development pattern, that it wasn't flexible enough, or it didn't recognize the need for flexibility, and didn't perhaps recognize in a strong enough manner the need for addressing the non-congruence between the life cycle of drugs and diagnostics.

I think that that wasn't the intent of the document, but that's the way the document read,

and that's something that does need to be addressed. The work plan is to take the concept paper, which is really quite a preliminary scientific document, and convert it into draft guidance. That would allow for a second round of comments, and then the draft guidance would become final guidance.

I won't promise this time course because we missed the last one by a couple of months, but there was at least the intent. We will try and get the draft guidance out by the end of this calendar year.

There is also some specific guidance, actually the guidance of Dr. Mansfield, who is sitting to my left, originally worked on when we were lucky enough to have her, which started as sort of a multiplex document, and now is more focused on genetic and pharmacogenetic tests. That document is more specific, certainly more diagnostic specific, and is in the final stages of review. I, again, don't promise it will come out this year, but I hope it will come out this year.

We continue to explore changes in guidance and changes in regs to clarify what is still a rather messy area. Actually about two weeks ago, and I want to thank Carolyn Jones who is also in the audience, AdvaMed actually submitted a frequently asked questions document that for us, and probably for them as well, was somewhat unprecedented in that the document and frankly private entities both in the trade sector and in the professional sector frequently provide us free advice and offer us guidance documents which we will sometimes laugh at and sometimes in fact embrace, launder, and then use.

But the effort in the AdvaMed frequently asked questions was one in which there was an effort to clarify the world of ASRs and was very unique in that AdvaMed actually reached out to the laboratory community and tried to get input from the laboratory community as well. So it's a very interesting starting point. They have put it officially on our docket, so I believe it's public. We do plan to steal the document probably to launder it and to try and use it as a basis for draft guidance to help clarify this colorful world.

It is a nuanced document that's missing some pieces. We might plug in those missing

pieces, or try to at least. There continues to be a background of confusion and either inadvertent or deliberate misuse of ASR and home brew offering tests. Some of the home brew tests are actually going in ways I think even SACGT might not have predicted, some interesting ways.

So we are interested in continuing in a modest way to explore whether there are incremental changes in either the ASR exemption or the position itself. There is, as I suspect everyone in this room knows, a new face to the FDA administration. We have a new acting commissioner, we have a new head of general counsel, and we have a variety of new leaders in the deputy position in the Parklawn Central Commissions Office.

As far as I know, they haven't been asked the litmus request about abortion testing, and they also haven't been asked the litmus test about ASRs or home brew. So I have actually no way of predicting how any of this will come out.

Deborah Wolf was also sitting to the left of me. She's from the Office of Compliance, but we do operate as one operational unit in CDRH to take the lead in an ad hoc group that was a spinoff of this group to look at the colorful world of direct-to-consumer testing of genetic tests.

The notion was that FDA regulation of particularly the home brews, but even of the cleared and approved devices themselves is perhaps not the strongest regs that have ever been written in the history of U.S. regulatory authority. We were going to try to leverage off of FTC.

So we did put out a call for websites. We did get very interesting websites where there was direct-to-consumer testing, but we found this task to be much more challenging than we would have guessed. We were looking for two criteria. It had to be outrageous, but being outrageous wasn't enough. It had to be both outrageous and potentially harmful, because that's the way we interpret FTC's charge. Just being outrageous, fraudulent, or weird is not sufficient.

We actually had identified a couple of candidates, one in particular that we thought

would be interesting to test the water. We had argued about how to craft the language so it would be friendly to a person who might not be a scientist. Actually, as only FDA can do, through several iterations, we were about to launch it to format when we noticed that either because of the business realities that were in the background, or maybe because FDA kept looking at the site, the site went out of business and put up a for sale sign.

(Laughter.)

DR. GUTMAN: Then at least one or two other sites that we were actively interested in started to change the tone of their advertisements in ways that made it seem to us that they were becoming more elusive.

So my request to you as a workgroup, not Emily's subgroup, but the workgroup, or frankly the audience as a whole, is if you have any favorite test you think is both outrageous but also dangerous that would be useful to us, this committee does exist. We are anxious to give Matt a little bit of extra work.

Mary Pastal on my staff and I both spent -- I was on an FDA-identifiable computer and she went on an anonymous computer, and we spent several hours one afternoon hunting, and maybe we didn't put in the right buzz words, maybe we're so stupid we don't know how to, you know, put DNA and test, or OTC and test, or DTC and test, or home use. We just couldn't find anything that piqued our interest. So I was surprised. Maybe we were just looking in the wrong places. This is an all points bulletin for help.

Two final notes. The diagnostic industry from my perspective has I think, probably a little bit rightfully, a sense of disenfranchisement, because pharma is bigger than they are, drugs makes a lot of money, and drugs are bigger than we are.

I had talked at an earlier meeting about our efforts to set up some kind of workgroup that might represent the old Pharmacogenomic Roundtable and be a little bit more distinctly IVD in orientation. I

do think this committee -- and certainly I think we in drugs and diagnostics do appreciate a sort of shotgun or matchmaker role here in trying to bring culturally different companies together. Joe Hackett has set up a working group within our office, and is having active negotiations with Carolyn Jones and others in the industry. The notion is that we will, and I had hoped that we would have had this done by now, but there are a lot of competing demands on both industry's plate and our plate.

We do hope to at least explore whether there are opportunities for industry and FDA in a very diagnostic-specific way to describe the unique challenges that are on the table. And then it is worth noting, and I apologize I missed at least part of yesterday's activities, there really are fertile areas of development in ongoing work, that CDC has at least two initiatives. Muin's EGAPP and also Joe Boone's work in the area of trying to get material quality controls.

NIST has an activity where they are looking at now standards for proteomic testing, and AHRQ recently had a genomics workshop. They don't have a lot of money, but they have a lot of good ideas where there is interest in trying to step in and look at outrageous evidence-based medicine and outcomes.

Allen?

DR. RUDMAN: Maybe I'll come up there and present.

DR. WINN-DEEN: Do it from wherever you're comfortable. If you're comfortable where you are, you can just say next slide, and they'll do it.

DR. RUDMAN: I'm going to go through these very quickly. This is actually a subset of the slides. We're going to go through them very quickly. Part of this is you'll have the documentation here, so you can go back and review it.

I'll start off with the FDA's mission. It is really to protect and advance public health by helping to speed innovations and make medicines and food more effective, safer, and more affordable. This is really reflected in the critical path initiative.

Next slide. Thank you.

Towards that end, there was a publication, "Innovation, Stagnation: Challenges and Opportunity on the Critical Path," that was issued under Dr. McClellan and Dr. Woodcock. This kind of gave the overarching description of really this initiative.

In addition to that, there was an NCI and FDA joint program to streamline cancer drug development developed by Dr. McClellan and Dr. von Eschenbach, who is now in the FDA. Towards that end, one of the goals was developing markers, biomarkers, for critical development in evaluating new cancer medicines.

This is in November of 2003. A draft guidance came out, genomic data submissions, which created a whole new paradigm for voluntary genomic data submissions. What the FDA had found was really we had not received a whole lot of genomic information from the industry, although we knew what was going on. We had anecdotal information indicating there was a lot of research going on, but we really had no access to it.

The companies were not submitting it as INDs, NDAs, so we knew there was something coming up. The question is how to get that information and work with it, and figure out how to deal with it for the future.

Towards that end, we created this whole process. It really formed around the interdisciplinary pharmacogenomic research group. The goal here was to get companies to submit to a voluntary or required genomic data submission, track it, meet with the companies, find out what they're doing and why, process it, and then there were three major goals.

One was kind of public feedback. Conferences, workshops with industry, with the public, NIH, and so on. Data knowledge, and leading to guidances and policies. How do you know when to get the information? How do we work with it? What do we do with it? And finally, education, both internal

to the FDA because there is not a whole lot of mass there in terms of education, and also external. This was all under the construct of the Critical Path, really.

The IPRG, I'm going to use that because otherwise we are going to be here more than 20 minutes, was created, and it represents representatives from the entire FDA.

Along with that there is a group called the Pharmacogenomics Working Group, which is actually just located in the Office of Clinical Pharmacology and Biopharmaceutics. They have numerous activities, and I'll just briefly go through them.

One is the actual view of genomic data submissions, of which we have a large number now. I'll go into that a little bit later. Required submissions, consults, policy development, which Dr. Gutman just mentioned about the drug/device combination concept paper, education, both internal and external, research. There is a CRADA on biomarker validation, clinical trial protocols, how to design them, analysis of labeling, Pgx, pharmacogenomics.

There is a research grant out there, I am the principal investigator for that, looking into putting all this information, there are actually over 50 labels out there containing pharmacogenomic information, but some of it is more useful than others, and we're really trying to put this together as a useable database.

Finally, there is the information technology area. The FDA is developing software. RateTrack is one of them. We are also looking at database development. How do you get to use this? This goes to the question of knowledge management.

This is a slide of the IPRG organization. You'll notice at the top it's really driven by the FDA. Actually, that's the main message here. This is not a CDER initiative or a CDRH. It covers all the centers that are relevant. NCTR, Office of the Commissioner, CDER, CBER, and so on, and then there is a whole organizational chart.

The chair of the IPRG is Dr. Felix Freuhx. It has center delegates at a fairly high level, division office director, that type of thing. Then there is a whole series of activities associated around that.

I'm not going to spend a whole lot of time on this. There is a whole process involved in this, which you could find on a website.

The guidance was actually finalized in March, 2005. We have received 23, 24 today, we received another one yesterday, voluntary genomic data submission requests, and have scheduled to hold 12 already. These include two joint FDA European Medicines Evaluation Agency meetings, briefings, joint meetings. I'll talk about that in a few minutes, including multiple VGDSs and different drugs and follow up submissions on the initial study.

So companies are coming back to us with follow up information, and coming back to us with the different types of submissions, which is actually very helpful and very useful. It really tells us that we're doing something right.

We expected to see a lot of cancer drugs, and we saw that. But as you can see, we have seen a lot of genomic information, a lot of different areas, including different types of cancer, Alzheimer's, hypertension, hyperglycemia, depression, obesity, and rheumatoid arthritis.

We have also seen a lot of discussion on a lot of different areas. I think this is probably not as clear. One is the whole question of biomarker development. But then we get into the questions of genotyping devices, microarray analysis, validation, analysis software, the assumptions under them, databases, metabolic pathways, biostatistics, and enrichment design, clinical designs and clinical protocols.

This is a fairly broad, fairly comprehensive discussion, and it covers a lot of areas. It's actually changing the way the FDA looks at how we do things.

A little bit about the harmonization. Most of the large pharma companies are global. This is really becoming more and more important, this joint effort and consistency among both Europe and

the United States. Eventually it's going to be Europe. I think there are initial meetings now scheduled for ICH.

On May 17th we had our first joint FDA/EMEA, that's European Medicines Evaluation Agency, meeting. It was by video conference, obviously being the London and Washington area. As you might imagine, there's a lot of preparation involved in this, including the list of questions that we are really being asked about.

So there was a lot of interaction before the meeting, including in-depth scientific evaluation, sponsors questions and information, dialogue between the FDA and EMEA. We obviously operate under different regulatory environments.

We are very fortunate, the sponsor provided excellent presentation. It was really a good discussion on a lot of different issues, including registries.

One of the novel things about this is we are issuing joint minutes on these voluntary genomic submissions. Just as important, maybe more important, is that the FDA and EMEA evaluated with only minor differences the submissions. Nobody had done this, so we really weren't sure what we were going to hit on this, but it turns out, at least in this case, we were fairly consistent.

We both had to adjust our usual format. EMEA actually, apparently this was one of the first times they had issued written comments to the company. Very positive response, and clearly it is the first step towards harmonizing.

I should add there are three more meetings scheduled, being scheduled. One of them definitely in December, and then two more next year, in 2006. So this is a fairly positive development.

Another area is what do we do with all of this information? Part of it is obviously we issue guidances and concept papers. This is the list, I'm not going to go through this. You'll find these on the genomic webpage. If you go to that, there's a lot more information. I'll give you that information, where to

locate that later on.

This is not just the FDA, really this is about building a process with the industry, academia, and NIH. There have been a number of different workshops, public workshops I should say. It started off in 2002 with Workshop #1. That's what they named it. Creative. What am I going to say?

Then there was a draft guidance on genomic data submissions. This has been followed by a whole slew of other workshops, including the FDA/DIA Pharmacogenomics Workshop #2. This is where we really discussed the draft genomic data submission guidance. I actually got a lot of input. This is all done with PhRMA, BIO, the Pharmacogenetics Working Group, which is a collaborative organization, and others.

In 2004, there was a meeting on the co-development on drugs, biologics, and devices, and AdvaMed was a cosponsor, along with the MDMA. It was a docket to get comments, and we received quite a number of them. Actually, this fed into the concept paper, and ultimately into the guidance.

This year there was a third workshop in a series optimizing the benefit risk of drug development therapy. As you see, coming along more and more, this has been coming from the research side into the regulatory side. Again, it was with PhRMA, BIO, the Pharmacogenomics Working Group, and a lot of others.

Finally, just this October 6th and 7th, we had another workshop on the application and validation of genomic biomarkers for use in drug development and regulatory submissions.

I'm going to talk about this. Why don't I just go to this. If you liked the handout from DIA, these are some of the topics on keynote addresses. I'm not going to go through this, except to say it was well attended, over 200 people, people like Dr. Woodcock and others, talking about really where this is going. Ultimately pharmacogenomics kind of is part of the whole biomarker question, which probably proteomics is next in the line, imaging, and so on and so forth.

But how do you do this? How do you actually get to the stage where you can actually implement this? What do you actually need to do to validate these? So if you look at the topics that we've covered, safety biomarkers, efficacy biomarkers, I'm sure that more and more we're getting toxicogenomics submissions into the VGDS process. That's the one that you received yesterday. So more and more we're receiving large amounts of toxicogenomic data.

Update on the HL-7s, the definitions. As it turns out, that's going to be very important. Even the use of the word "validation" is apparently somewhat controversial.

Electronic Submission Working Group. Standards for developing safety and efficacy biomarkers, validation of these, introduction of how do you actually introduce these into the drug development process? What are the regulatory implications of it? Developing and validating genomic biomarkers, databases and so on. You can read it.

This is kind of like an overview. I like this slide, it puts it into a context rather than just listing all of these, about where we are and how we are doing. The big arrow is really you can use it in a number of different documents.

It goes from basic research to FDA approval, and all the different steps in between. There are a number of different versions of this. But if you look in the bottom, these arrows, actually it turns out this is really what we're talking about.

When you start doing the analytical validation, what does it consist of? How do you do it? What are the criteria? The preclinical feasibility, the clinical validation, and also the clinical utility? The fact that you have a test doesn't necessarily mean it's going to be useful for actually public health reasons.

At this meeting, actually Chris Webster from PhRMA, who works for Millennium, presented this slide. I thank him for this. He announced that PhRMA is going to propose a consortia on biomarkers. You can read it for yourself. The goal here is to expedite biomarker development. They are

expecting, hoping actually, that the FDA and NIH will participate, as well as a lot of other organizations.

We are looking forward to this. We actually don't know a whole lot more than what you see there, but obviously this is an important outcome of the workshop.

Finally, concluding remarks. One is I think the VGDS and pharmacogenomics programs at the FDA have been quite successful. FDA has been a regulatory lead in numerous areas, including guidance development, analysis of pharmacogenomic data, international collaboration, and obviously the workshops.

The VGDS submissions have provided FDA with really a wealth of significant genomic data and information and numerous therapeutic, scientific, and technical areas which would otherwise be unavailable. So in that sense, the guidance really was successful.

The pharmacogenomic research needs to be seen in the context of biomarker development and validation, as well as disease management to expedite the approval of new drugs and indications.

It is not just about finding the drug, it is actually getting it to the public. It has to go through the FDA really to do that, and the need to provide the FDA and industry can readily analyze which expedites review. This is about not just finding the biomarker, not just increasing public health, but how quickly we can do this. How quickly we can get these drugs to the market.

I would like to add FDA does not develop drugs or pharmacogenomic tests, but it can encourage them to be developed. Finally, I would encourage this committee could help as a group by recommending the formation of a task force to develop national standards for pharmacogenomic assays. Thank you.

DR. WINN-DEEN: So I want to thank both of you very much for your --

DR. RUDMAN: And finally, there was a website.

DR. WINN-DEEN: -- speedy overview of what's going on at FDA. We obviously should have allocated a little more time for the "update."

I had one question for you, Dr. Rudman. When you did this joint program with EMEA, was that at the request of a particular drug sponsor that you do that? Or was this something where you sort of got together and said we ought to pick a project and see if this would work?

DR. RUDMAN: You're talking about the CRADA? We had an interest in this, and so did the company. We found through one of these interactions that we had a common interest, and that's really how it came about.

DR. WINN-DEEN: Okay.

DR. RUDMAN: They were doing biomarker development, and we were interested in this, so CRADA came out as a natural outcome of that.

DR. WINN-DEEN: Is there a mechanism for companies to do that on a regular basis? Or are you working towards that?

DR. RUDMAN: Well, they can actually submit them. We have a website, we have email addresses, and people call us all the time and ask about these things. So we are very receptive to them.

We do have limited resources. We can't do an infinite number quite clearly, but we are very interested in continuing on with this process.

DR. WINN-DEEN: We have maybe 10 minutes for Q&A. I've got Julio and James, Kevin and Agnes.

DR. LICINIO: Just following on one of the things at the end on the need for national standards for the testing, which I think is crucial, because we discussed a lot both here and in different contexts this issue of what do you do with the test result, the privacy, and this and that.

The issue is what is the best to begin with, which is kind of a very crucial issue. We

discussed this informally before the meeting began. Not only is there no kind of national guidelines or licensing board for that, but if such an entity were to exist, where would it belong?

Is it in the purview of the FDA? Of the CDC? Who would be responsible for monitoring for issues like, you know, a standard of quality control, ensuring that it meets that kind of standard?

DR. RUDMAN: That's a very good question, and actually a very complicated one. You are really asking a number of different questions, and I'll try to address them.

One is it is not just about the validation. Actually, that's part of the issue. There are numerous types of validation. Is the test validated in vitro? Are the labs performing it correctly? I mean, this is kind of a CLIA question.

Does it work in humans? Is it clinically validated? And finally, does it have clinical utility? I mean, the fact that the test works doesn't mean the public health would be necessarily improved by it.

So all of these, these are all questions. So you have to kind of parse these out. The first step before you can even get to enforcing these, and there are processes in place such as CLIA, is really to define what you mean. That's what we really need to start doing, get some consistency on this. Then I think we can assign responsibilities accordingly.

DR. GUTMAN: Let me just augment that response, because at least for the diagnostic industry, there really is a premier standards crafting group, that's the CLSI, the Clinical Laboratory Standards Institute. So if you were able to subsume drug issues, the most logical place to turn to for standards in this country at least is CLSI.

CLSI is also the Executive Secretariat for the international standards group working in the area of labs, ISO CT212. So you technically have capacity to kill two levels of standards with one stone in turning to CLSI. Again, they are focused largely on the diagnostic issues, and so there is no reason they

couldn't be a little more inclusive. They wouldn't start creating pharmacology standards.

DR. EVANS: I'm naive as to what the purview of the FDA is and all of its manifestations. I was wondering if you have anything to do with guidance of how results are reported.

The reason I ask is that I contacted Roche, and I asked for a sample of a report from the Amplichip, and it was really completely incomprehensible. I'm a geneticist, and I do pharmacogenomics.

So I worry greatly about the access to this information in an understandable way to clinicians, and I'm really glad that you brought up twice the issue of a difference between clinical validity and clinical utility. It goes beyond public health into the individual as well.

Unless we have understandable types of reports, then the utility and validity can really get blurred. I was just wondering if the FDA has any role in that.

DR. GUTMAN: The FDA in general does not regulate the reporting system itself. We will sometimes be concerned enough about some aspects of the way information would be reported out that we'll try and push the limits on it, but we don't have direct authority.

Unfortunately there's no one from the CLIA program -- do you know, Muin? Does Judy Yost have the capacity to tell a lab? I mean, there's the expectation, CLIA clearly has both pre and some post-analytical requirements. I actually don't know, but we can certainly take that back and find out what their authority over that is. I assume they have some, but I don't know how strong it is.

DR. KHOURY: I'm not sure how much they have authority, but I can tell you one thing. CDC, the CLIA group that works with the CMS program, has looked at genetic test reporting in general and the variations around that. Not necessarily in pharmacogenomics, but in other areas. There is quite a bit of variation in genetic test reports. That was a project that just got finished.

I think the SACGT, I guess our parent group here, kind of took on these issues for I guess a couple of years. They tried very hard to sort of develop an overarching package for the oversight of

genetic testing and the transition from research to practice. They came up with very thoughtful comments about the need for three or four processes.

One as an FDA-driven process, which I think FDA has kind of taken over the last couple of years and struggled through. The second is a CLIA-driven process, which includes the development of genetic testing subspecialties.

These have different arms. The third is sort of more voluntary, what we call a public health related effort for developing the kind of data that is needed from a non-regulatory process. This is something the CDC and others have worked on for the last few years, that kind of led to the EGAPP initiative that you heard about yesterday.

So we are all moving in some direction, but I think there are just too many gaps right now in that process. I think pharmacogenomics is uncovering some of these gaps, and this committee could sort of take it on again.

DR. WINN-DEEN: So Kevin passed his turn, and Agnes is going to be the last question before the break.

MS. MASNY: Thank you. This is a good segue, I think maybe some of what Muin just said would cover some of the issues that I wanted to just bring up regarding the education.

Really thank you very much, because it was exciting to hear all the numerous initiatives of the FDA in moving forward in this area of pharmacogenomics. But yesterday we did hear from some of the speakers regarding our concerns about launching large population studies suggesting that one of the major barriers was the lack of genetic literacy from the public in agencies such as the FDA, as well as in the health professional community itself.

So I just wanted to say that I think that some of your responses show the definite movement in that area sort of lessens some of my own concerns about that. But at our last meeting, we also

had some updates on pharmacogenomics, and one of the presenters talked about the use of TPMT testing for children who would be treated with 6-mercaptopurine, and also brought up that there was a lack of the use of that testing because the clinicians, even with the labeling and things like that, were not sure of how to use it, or maybe had other concerns about liability.

I know in your slide, Dr. Rudman, you had education initiatives, both external and internal. If you'd comment a little bit more both on what education initiatives are going on within the FDA and possibly for the community, health care provider community to make use of some of these tests, that would then come out.

DR. RUDMAN: This is a very good point. Internally, actually we've started a whole series, I think there are three or four of them now, of internal FDA seminars and training sessions. We have also brought into the process as part of this whole process, not only is there formal training in the FDA in terms of teaching people about genomics, about different types of software and so on and so forth, these types of formal training programs, but we're also bringing reviewers and their division directors and management basically into these meetings more and more to try and get them to understand the issues and actually get their feedback on some of these issues.

So internally, we have internal websites, we have training programs, we have presented I don't know how many times already to different divisions in different areas to try to do this. I'm sure CDRH has similar type of programs in addition to this.

Externally, a lot of our effort has been through really two mechanisms currently, because of resource limitations, actually. One of them is workshops. We do a whole slew of workshops. We try and invite people to participate. You saw the list up there. But a large part of it is also through our website, which I have the website address up there, to try and get people to really understand these issues.

Some of these are fairly eclectic and difficult to understand frankly for the layman. In

terms of going outside, we have had preliminary discussions with some people, universities, about moving forward on this. We have also talked to the American Association of Clinical Science about setting up programs.

We don't actually have the resources to go physician to physician obviously to do that, but we do recognize a need, and we are trying to move forward on those issues.

DR. WINN-DEEN: Can I just ask a follow up to that?

DR. RUDMAN: Sure.

DR. WINN-DEEN: Do you think clear direction in drug labeling and package inserts would be helpful to physicians? I mean, I think right now when you just say by the way, this is metabolized by this enzyme, that really doesn't provide the physician with any real guidance, to be frank.

DR. RUDMAN: Well, actually, you have brought up a very good point. It is a difficult issue in some ways, and in some ways it's very simple.

We start off at the beginning, and that is actually what this grant is really about, in order to actually categorize this. When I tell people there are about 60 or more labels out there with genomic information, a lot of people are actually surprised at this.

Most of it is the CYP P450s. Some of it is more informative, and we're finding that the labels that are recent are more informative than previous ones. Some of these are fairly -- it's not always clear.

For instance, it's a TPMT issue that has been brought before an FDA advisory committee. Actually, that's part of how the outcome was generated. In terms of how physicians see this and how the FDA sees this, there are different proposals out there.

So a lot of this is bringing these before these advisory committees to get their input.

DR. GUTMAN: Well, it's a glass half full and the glass half empty. You have to realize

I'm a clinical pathologist, not a geneticist. If I were to survey what is going on in lab tests, or if you looked at the recent activity that CDC has initiated with the Institute for Quality and Laboratory Medicine, the average physician doesn't know how to order a prothrombin time, so I can't imagine the average physician would actually know how to order a genetics test.

The issue of ignorance in laboratory medicine, the appropriate use of laboratory tests, transcends the genetics issue. It is a core issue. If you look at medical school curriculums and clinical pathology, it is frightening, horrifying, disgraceful.

If you as a group, I just don't think you can underestimate -- I doubt the average practicing physician at a fine academic medical center would have understood my hurried explanation of predictive values, because they wouldn't know a predictive value if it bit them in the nose.

So this is an area that is replete with opportunities for improvement. Genomics or genetic testing would be a great way to start. I certainly hope that if you made recommendations to fix this problem, you wouldn't stop there.

DR. WINN-DEEN: Okay. I think that's probably a good place to pause for our break.

(Laughter.)

DR. WINN-DEEN: You know, if people feel the need to talk further with Steven and Allen, they are there. Before they escape out the door, we can probably get a few more questions answered.

We're going to take a 10-minute break and be back at 10 to 11:00.

(Recess.)

MS. BERRY: We're set to begin with the public comment section of our session. I'd ask that everyone be seated please so that we can begin the next section.

Let's get started, folks. One of our critical functions here is to serve as a public forum for deliberations on the broad range of human health and societal issues raised by the development and use of

genetic technology.

So we greatly value the input we receive from the public. As you know, we set aside time each day of our meeting to hear from the public and welcome and appreciate the views that they share with us.

Today we will be hearing from Jean Jenkins, the International Society of Nurses in Genetics, ISONG.

DR. JENKINS: Good morning. I'm Jean Jenkins, and I value the opportunity to be able to present to you today the following public testimony on behalf of the International Society of Nurses in Genetics, or as you commonly know them, ISONG.

I also want to inform you about an effort of several federal agencies, including the Human Genome Research Institute, Office of Rare Disease, Health Resources and Services Administration, and the CDC in collaboration with the American Nurses Association and ISONG to address genetic and genomic competency of all nurses.

We have provided the written testimony, and at some points I may refer you to that document. As you know, genetic and genomic science is redefining the understanding and the continuum of human health and illness. Therefore, recognition of genomics as a central science for health professional knowledge is essential.

Options of care will increasingly include genetic and genomic information along the continuum of care for all persons, including prevention, screening, diagnostics, prognostics, selection of treatment, and monitoring of treatment effectiveness.

The clinical application of this knowledge has major implications for the nursing profession, and it caused essentially all conditions have a genetic or genomic component. Recipients of nursing care will be from any stage of life, and cared for in varied clinical settings.

You will hear of a number of different examples where pharmacogenomics information will be used in determining how individuals respond to drug treatments. I won't outline those for you today, because I know some of the presenters will be discussing those.

With that kind of information and the selection of specific medications based on an individual's genotype which has major implications for nurses, they must be able to competently integrate genetic and genomic knowledge and implications into health care delivery so that all individuals receive equal access to genetic and genomic health care.

The code of ethics for nurses which was developed by the International Council of Nurses and the American Nurses Association state that nurses have a shared responsibility with other health professionals and society to ensure initiation and promotion of community, national, and international efforts to meet the health and social needs of the public.

This includes the right to seek and receive genomic health care that is non-discriminatory, confidential, and private. As providers in all practice settings, nurses must be able to advocate for and fulfill a central role in the assessment, the policy development, and the assurance of universal access to genomic health care, including discrimination by all populations, regardless of genetic and genomic literacy, socioeconomic, or ethnic/cultural background.

ISONG recognizes the application of genetic and genomic practice at both basic and advanced practice levels. Genetic nursing is the protection from promotion and optimization of health and abilities, prevention of illness and injury, alleviation of suffering through the diagnosis of human response, and advocacy in the care of genomic health of individuals, families, communities, and populations.

Nurses can fulfill these responsibilities by the identification of genetic and genomic risk factors, nursing interventions, information provision, services referral, and promotional health behaviors to enhance the health and well being of the individual or the family seeking care.

To fulfill the right of the public to access genomic health care without fear of discrimination, the nurse's responsibilities extend to the development with partnerships of stakeholders such as patients, health care providers, insurers, government officials and legislators, enlisting such outcomes of such partnerships are included in the written comments.

The public will increasingly expect that the registered nurse will use genetic and genomic information and technology when providing care, and these expectations have direct implications for the RN preparatory curricula, as well as for the 2.5 million practicing nurses.

The rate of progress for applying a genomic approach through the continuum of care depends not only on the technologic advances that we've been discussing, but also on nursing expertise.

In its report on genetics and nursing in 2000, an expert HRSA panel emphasized the importance of integrating genetics content into nursing curricula in order to provide an adequately prepared nursing workforce not only for today, but also for the future. To assume this role with persons, families, communities, and populations throughout the life span, the registered nurse will need to demonstrate proficiency with incorporating genetic and genomic information into their practice.

Examples of such indications of practice are provided also in the written comments. Under Tab 3 of your handouts, there is an indication of the collaborative meeting that I had mentioned at the beginning, which was an effort of several federal agencies, including NHGRI, CDC, HRSA, and the American Nurses Association and ISONG, where we provided an opportunity together for key nursing stakeholders to attend the meeting in September, 2005.

This meeting was held in Washington, DC, and representatives of key nursing organizations came to consensus, which is a major advance in the profession of nursing, on a document whose purpose is to define essential genetic and genomic competencies for all registered nurses.

This document is intended to guide nurse educators in the design and implementation of

learning experiences to help students, learners, and practicing nurses achieve genetic and genomic competency. These competencies are not intended to replace or recreate existing standards of practice, but are intended to incorporate the genetic and genomic perspective into all nursing practice and education.

The goal is to prepare the nursing workforce to deliver competent genetic and genomic focus nursing care. The essential competencies require that all registered nurses integrate genetics into their professional responsibilities, including the professional practice domain, nursing assessment, identification, referral, provision of education, care, and support. These competencies are listed in your document as well.

In closing, ISONG views genetics and genomics as integral to all nursing practice. Nurses will increasingly use genetic and genomic information such as pharmacogenetics and genomics to create and administer individualized treatment and care plans.

All nurses share in the responsibility to assure that all individuals have equal access to this kind of based health care, and that it is non-discriminatory. Thank you so much for the opportunity to share with you the progress that is being made in the education of nurses that begins to build upon this infrastructure that was mentioned yesterday as being key to be able to translate scientific innovations that we are witnessing into health gains for all. Thank you.

MS. BERRY: Thank you very much for your comments. I appreciate it.

Emily?

DR. WINN-DEEN: So now, Pharmacogenomics, Part 2.

It is my pleasure to introduce our first speaker of the next session, Tom Metcalfe. He is the head of the biomarker program for Roche Pharma. Tom has the unique perspective of also having worked on the diagnostic side of the Roche organization, and he is going to talk to us a little bit about how Roche as an exemplar pharma company is using biomarkers in their drug development process.

Tom, you can sit there if you want, or would you rather come up?

MR. METCALFE: I prefer to come up there.

DR. WINN-DEEN: You're actually much less intimidating if you sit down.

(Laughter.)

DR. WINN-DEEN: I should disclose that I used to work for Tom, and we were quite a pair when we went out in public together.

MR. METCALFE: Sorry if this is intimidating for you, but this is usual for me. So thank you to the committee for the opportunity to present to you on this topic.

As Emily said, my comments today are based principally on Roche's experiences in this field, but we believe that much of our experience is relevant to the pharmaceutical and diagnostics industry in general.

What I'm particularly going to talk about is some of the process aspects, and I'll really then tease out the feasibility of integrating pharmacogenetics and biomarkers into drug development from an economic perspective.

I think this broad definition of biomarkers is an objective measure or evaluation of normal biological processes, pathogenic processes, pharmacologic responses to a therapeutic intervention, or responses to preventative or other health care interventions generally broadly expected or broadly accepted.

Obviously as a part of that, biomarkers can increase our understanding of drug metabolism, drug action, efficacy, safety, facilitate therapy response-prediction, and expand the molecular definition of disease and inform about the course of disease progression.

Obviously this broad definition includes all diagnostic tests, imaging technologies, and other subjective measures of a person's health status, and obviously all pharmacodiagnostic tests. Most of my remarks are going to be focused on novel markers, either newly discovered markers, or markers which are being validated for novel applications.

So just a little bit about what's new, what's changing. Obviously genetics, genomics, proteomics, modern imaging techniques under the technologies allow us to measure many more markers than we could before. There is an improved understanding of the targets of pharmaceutical interventions, signaling pathways, metabolism, and mechanism of toxicity, and this will allow us to make more sense of the biomarker data that we're looking at, and biostatistics and bioinformatics allowing us to collect, store, and interpret this data more effectively.

Nonetheless, there is a tidal wave of data which we are generating, and it takes a lot of time and energy to interpret this effectively.

So again, how is this affecting pharmaceutical development, and particularly the integration of biomarkers and pharmacodiagnostics into drug development? These new marker data are allowing us to make considerably richer decisions in late research and early development. This is about which projects to move forward, and what the comparative, I suppose, prospects of different molecules in the pipeline are, but this is essentially an evolution of what we currently do with pharmacogenomic and pharmacogenetic markers.

Unfortunately, there is yet as few validated surrogate markers which allow us to run considerably short at trials. I think quite rightly, the status of a surrogate marker for a clinical endpoint is set very high, and there is a lot of evidence needed for us to reach the status of a validated surrogate. This will mean that it is going to take some time until we get considerably more surrogate markers and are able therefore to run shorter trials.

There are also as of yet very few highly informative response markers which allow us to run smaller trials or enrich our trials to potential responders. So we see this as being a steady evolution of the drug development process rather than a revolution, particularly because the first part is an evolution of the current paradigm, and we have few examples of predictive markers and of surrogate markers.

The various utilities that we see for biomarkers and novel genomic/genetic markers in drug development are pharmacodynamic markers which confirm biological activity, enable us to make early decisions on progressing molecules, and make optimization of dosing and scheduling more efficient, prognostic markers which correlate with disease outcome, and these enable or improve our ability to design informative trials and to interpret these trials competently.

Disease-specific markers which correlate well with the presence or absence of a disease. In some cases, these can be used to identify disease subtypes that are more amenable to one therapeutic intervention than to another, and can be used to enrich our trials for those most likely to respond. I think this is a very useful utility which we are beginning to use more. As you can see, this is not directly related to the action, efficacy, or safety of a particular drug. These are disease-specific markers.

The last category are predictive markers, such as HER2 overexpression in breast cancer, which correlate strongly with the activity of our drugs. Depending on how strong this is, we can include this in our trial design.

So this could lead us to come up with one possible classification of novel biomarkers with disease markers, pharmacological markers, and predictive pharmacodiagnostics set out like this. Obviously there is an overlap between these different sets. Some of the disease markers are predictive pharmacodiagnostics, as with HER2, but many are not.

I think it's very important that we begin to tease apart these different utilities and whether or not a disease marker can be used as a predictor pharmacodiagnostic. In our experience, in many cases these disease biomarkers lack the specificity to be used as predictive pharmacodiagnostics.

So I'm going to focus most of what I talk about about predictive pharmacodiagnostics, and especially with relation to the impacts on the economics of drug development.

Pharmacodynamic and prognostic tests tend to increase the value, or if you integrate them

into drug development, they tend to increase the value of that drug development principally because the size of the market that you're addressing is not really affected, revenues do not decrease, and they may increase because we can improve dosing and dose scheduling, and investments in markers generally are offset by improved decisionmaking, trial design, reduced attrition, and therefore beneficial in general.

I don't think pharma companies have any issues at all including this work in theirs, or these sorts of markers in their drug development work, because it's generally beneficial.

The value impact of predictive markers is less clear. They may reduce the size of the market. This reduction in the size of the market may be offset by improvements in market penetration, increased average duration of therapy, and potentially in pricing. I think the pricing point is what we need to look at, because obviously this is only relevant if this is done before the pricing is set within the market. It may also improve the competitive position of the drug. But I think the most critical thing about this is it depends upon exactly what we're looking at, and it requires careful case by case analysis.

I'll take you through some of the analytical components later on to show you the complexity of it.

Now, looking particularly at the application for response prediction, this is a prototypic concept for the application of these sorts of markers, and it is schematic, but I think it also teaches us some important lessons.

The first thing that one has to do if one is going to include response markers in a drug development program is to have a reliable understanding of first of all, the biology of the marker, and then also the test that one is using to test for that marker.

So we generally have to spend considerable time in early drug development and biomarker discovery, and then work up those biomarkers into reliable tests, invest time in biomarker test development and validation, and then as we start introducing the drug, to collect samples and store those

samples.

The most informative time in early development is going to be Phase 2, because in general, Phase 1, or in early clinical development, there is a lack of conclusions that one can draw. One generally begins to be able to draw conclusions about whether or not a drug is working or not at the end of Phase 2.

So if one knows which biomarkers one wants to look at, has been able to develop a test, then it's possible to do a retrospective analysis of these biomarkers on samples collected in Phase 2 and correlate these with response, or lack thereof, or perhaps with safety as well.

One possible thing one could do is prospectively recruit the patients using biomarkers found to be useful at the end of Phase 2 in your Phase 3 program. But in order to do this, you'd have to have a very informative and reliable biomarker. In general, we find that it's very difficult to find biomarkers which are informative enough to have us take the risk of recruiting for a Phase 3 trial based on a response marker.

An alternative to this might be to balance the various arms of a trial to make sure that both arms are equally populated with patients who have a good chance of response using this marker. So this is I think one way of doing things, but currently we rarely run into the situation where we can do this at the moment. This means that we are therefore essentially not changing how we develop drugs. We are tracking more things, but we are not changing the trial protocols as yet, or in very few cases.

I think the one drug where this paradigm was followed was with Herceptin. This is the current diagnostic paradigm that is used to determine whether or not the patient is eligible for Herceptin therapy. There are two particular tests which are used. One is immunohistochemistry, which is basically testing a patient's tumor tissue, then if he has a result which needs further interpretation, one applies what is called a FISH test to that patient as well.

So that worked with Herceptin therapy. One of the reasons that worked was because the marker was informative enough. But now I'm going to sort of come onto some questions which arise if one wants to apply this paradigm broadly.

First is what is an acceptable response rate for a novel drug? One should think about applying a stratification with a response marker. If you go towards the end of this scale where you have a very low response rate, the first thing you start to question is whether or not you have a viable drug. It is only when you move up perhaps above the 10 percent response rate that you think maybe you could apply a response marker in your clinical development.

When you get above the 50, 60, 70 percent in terms of response, this is an excellent response for a novel drug. Again, you start beginning to think whether or not it makes sense to apply a response marker. So clearly there is some window of opportunity, and many drugs do fall into this category. But I think that's one set of questions which one has to ask.

The second set of questions which one has to ask is whether or not you're looking at response, or whether you're looking at safety markers. Clearly we believe that when you look at the balance between increasing efficacy of a drug and increasing safety of a drug, it is much more likely that we're going to be using this initially to be increasing safety of a drug simply because of the practical issues of predicting adverse events reliably. This is in terms of predicting adverse events. I think it's different if you're monitoring potential adverse events. But for predicting adverse events, it becomes very difficult, because these are likely to be infrequent events with a useful drug.

The third thing that one has to take into account is what particular indication you are looking at, and also what the balance is between efficacy and risk in that indication. Clearly in indications like cancer, there is a high utility of this sort of approach, because patients have a very great medical need, and one is prepared to take on perhaps more safety issues because of potential benefits than one would in

other indications.

A second set of issues that one runs into when you are looking at this is defining what you call response. As I said at the end of Phase 2, you're looking for responders, and you're looking to correlate these markers with responders. If you don't have a clear idea about what a responder is and what a response phenotype is, you can run into issues.

A recent example that we've run into is looking at patients suffering from rheumatoid arthritis where there are two accepted or broadly accepted, the ACR is the most accepted test of whether or not a patient is responding. The ACR response measure includes a level of acute phase reactants, and in a novel therapy, which we're using, we see it as being beneficial, but we don't see any change in the level of acute phase reactants.

So this again causes you to question whether or not you're looking at the right sort of responders, particularly because novel therapy interventions are likely to change what we call our response and what we call lack of response.

There are many different test requirements if you're going to be using a reliable pharmacodynamic test. Many of these are analytical, but there are also practical issues. You basically want to test which isn't particularly invasive, which has where you get the information out of the test in a relatively short time, and certainly where the value of the test information outweighs the acquisition costs of that information.

Obviously availability of that test is also important. One practical aspect of using it is in many cases, some of the novel markers that we're looking at do not have widely distributed testing platforms established in the market, and this is basically going to be a hindrance to getting wide uptake of these sort of tests in the market.

There are also other considerations in terms of the predictive value of that test and the

invasiveness. Certainly in our work we've seen that host genetic factors, it is quite easy to get information about host genetic factors based on pharmacogenetic tests, but there are limitations currently that we see with the predictive value of host genetic factors, principally because of the penetrance of many of the genetic factors that we're looking at.

Other host factors such as proteins, serum proteins, metabolites, and chemokines can be acquired out of blood tests, and infectious agent factors can also be acquired out of blood tests. Many tests that we would like to use require the use of tissue, and in many cases, it is very difficult. It's impractical to require a patient to give you a tissue sample in order to test for a predictive marker.

One exception to this is obviously in oncology where in many cases, one has access to samples from the primary tumor.

Obviously one also wants to look at the clinical utility of response prediction and trade off the risks and benefits related to an empiric approach, whether or not the response rate is, as I said, is closer to 100 percent or closer to zero percent, the relative predictive value, and issues related to market acceptance of practicality.

So in summary, some of the challenges around this are identifying the right biomarker early enough. I'll just go into in a couple of seconds some of the challenges around developing pharmacodiagnostic tests within drug time lines, and ensuring collection of enough of the right samples and defining the sampling conditions at the right time, storing the samples effectively, and also having a good protocol for the preparation of the test out of the test sample.

So I think if you have a validated biomarker, something where you know what the biological information coming out of that biomarker is and you have a good analytical test for that biomarker, essentially there are few issues to integrating this into a drug development. You basically just use the lab-validated diagnostic test during your pharma development, and you can use that in your filing

together with the drug filing. This shouldn't be a big issue.

It becomes more of an issue if you identify the biomarker, let's say in late preclinical work, and you have to work up a biomarker assay yourself. Generally what you will do is you will develop let's say a prototype assay, you'll then use this prototype assay during your drug development, and you'll try and then work up a commercial test for this, such that it can be introduced into the market, and you do a validation, a crossover validation between the commercial test and the assay in development, and hopefully you'll get good enough correlation that you can use this in a data file. So this is, I think this also works as long as you do the proprietary work in the right way.

It becomes more of a problem if you discover the biomarker either in late development or post-launch. One of the reasons is that you won't have a commercial IVD when you launch your drug, and the second reason is that you probably won't have been able to integrate this in your regulatory submission, and also your submission to pay your organizations, such that it won't be included in your pharmacoeconomic model.

This means that many issues arise when you run into this sort of situation. I'll go through some of those issues in a little while.

So I think one of the other things that we have to take into account about the incentives for pharma companies to do this is that all this work costs money, and pharma companies have to balance the investments that they make in biomarker work versus the investments they make in new medicines.

They'll do this as rational profit-incented organizations, they'll do this based on the incentives which are laid out in front of them.

So this basically summarizes what I've said, that in early development, pharmacodynamic and tox markers help, prognostic markers help, but in late development, we don't see many cases currently of therapy response markers which are predictive enough to allow us to recruit based on those. So this isn't

simplifying the situation currently. It does not make drug development any cheaper, and it's not making drug development any simpler.

In few cases do we expect to be able to use surrogate markers in place of endpoints, but we expect that increased use of disease markers will allow us to run more effective and efficient trials, and to differentiate our compounds in the market more effectively. We expect that these activities will lead to the development of innovative diagnostics and improvements in the practice of medicine, and this will feed back into improved drug development with time.

So I think I've been through most of the points on this slide. What I want to go onto is the impact of pharmacodynamics on key pharma value drivers. The value drivers that we see in drug development are basically the quantity of clinical candidates, new molecules which we can put into a pipeline. Here we essentially see that the impact of pharmacodynamics is mutual.

The quality of molecules which you have in the pipeline, and this is essentially measured in terms of success or attrition rates, and here we see us being able to improve the potential of getting a specific molecule out of the end of the pipeline by using pharmacodiagnostic tests simply because there are some tests which we'll be able to bring to market which we would otherwise not have been able to do.

Time also is another important value driver. This is the dwell time of a project or phase, and we see this as negative, because it takes time to integrate these tests, to interpret these tests, so this is going to be a negative impact on time. The overall cost per clinical compound brought into discovery will also probably be negative. It might not be very negative, but it will likely be negative. We think that the overall impact on project value for a successful project is likely to be positive.

So taking this all together, adding predictive pharmacodiagnostics to drug development adds cost, uncertainty, complexity, and the potential for value creation currently varies from project to project, and one has to make a project-specific decision.

If you think in terms of, this is just in terms of attrition rates, I think they might not apply to all pharma companies, but this is I think illustrative of the current situation. You have roughly a chance of somewhere between I guess 3 in 100 and 10 in 100 of drugs which you put in at the front end of your development pipeline coming out of the back end of the pipeline.

One of the goals of pharma companies currently is to reduce late phase attrition, principally because the cost per project increased significantly the later the phase. So I think one of the challenges we see with this work is if you are going to do this effectively, you basically have to integrate biomarker work with all the programs you have early in the pipeline, and that only a very few of these are going to be successful.

So all that work that you put in early in the pipeline adds additional cost, and you're not seeing any benefit in terms of the specific projects, or you are basically losing something like 95 percent of those biomarker projects because the drug isn't getting to market.

So this attrition rate that you have for drugs also applies to your biomarker projects. One of the important things that companies are trying to do is they are trying to capitalize broadly upon their investments in biomarker work by applying these throughout or to other compounds in a particular therapeutic area.

This chart is deliberately complicated, but it basically shows what the effects of pharmacogenetics and pharmacodiagnostics are on pharma value flows. You can see there are many different factors, which one has to take into consideration, and these have to be balanced off against one another.

You have major factors, minor factors, factors which some are positive, some are negative. I think this shows the complexity from applying these on a specific project in determining whether or not you are likely to get a positive value or a negative value by integrating biomarker work into your

pharma development project.

So the economic rationale for personalized meds, and I think this is clear to pharma companies, that there is a clear economic rationale, particularly from a societal perspective, that if you have targeted therapies where a drug is linked to a pharmacodiagnostic, non responders or poor responders are removed from the pool of users, and monetary and negative utility for adverse events are avoided.

Better targeting can lead to a greater volume of adoption by good responders, some of whom would not have used the drug previously, or may have discontinued use of the drug previously, and good responders may have improved compliance, and therefore, additional net benefits.

So the improvement of predictability of outcomes create additional value for patients as they essentially face less uncertainty. I think these economic rationale are very clear to pharma companies.

What is the value? This is just looking at innovative medicine in general. This is what very unspecific but obviously fully informed patients are willing to pay. We see the value as what patients are willing to pay based on these various benefits. So this is the value of innovation for novel drugs is what patients are willing to pay, broad societal value, and then obviously there is an innovative perspective. So how are the incentives aligned with working in this area.

So the personalized medicine, the economic value proposition to patients, as I say of a personalized medicine or targeted medicine, is to decrease the cost of adverse events, faster and more complete adoption, and hopefully improve compliance and greater predictability of outcome.

I just want to go through an example for you to illustrate this. If we look at a new drug which has a 20 percent response rate, this is towards the lower end of that scale I showed you earlier on, the company who is developing this has an initial price estimate that they can charge $1,000 per year for this drug, what our patient or payer is willing to pay for this, how much it is worth if you know who will respond and who won't, so what's the value of the reduction in the certainty, and what are the side effects.

So again, taking this example, if you have for this new drug a response prediction test, and this is I think, again, we have to see that this is entirely theoretical, because we're saying that we have a test which with 100 percent sensitivity and 100 percent specificity, accurately predicts the response to this new drug. We know that is entirely theoretical.

It is based on a readily detectable biomarker. So if we were to screen all potential patients and only treat those likely to respond, what would be the value of this? So it is clear to see what we expect to see happen here, that we would get a targeted indication. We would hopefully get based on who is responding and who doesn't respond, faster uptake, and improved competitive position. So what should the price be?

So with no test, we have, if you're looking at 1,000 patients and patients are willing to pay $1,000 per patient per year without the test, then the value would be 1,000 times $1,000, $1 million for the company who is selling this.

Now, if we have a perfect test, we have 200 patients, one could posit that the willingness of each specific patient to pay would go up six times because they don't have a 1 in 6 chance of responding, or a 1 in 5 chance, they have higher than that, and the incremental value that we see here over and above the situation without the test essentially comes from what we see as an additional value in reducing the uncertainty.

This reduction in uncertainty has a value over and above the case where one has to take a chance. So this lays out what we see as the potential value for this. Now, this, as I said, this is a theoretical case, but we believe the underlying concepts which we built into this case are broadly applicable. One can always argue about what the incremental value of the certainty is, but we certainly see that there is value attached to that.

Now, a lot of the value capture that goes on, that depends on the manufacturer's ability to

set price. This comes into then the economic incentives of companies to do this. So if the pharmaceutical manufacturer cannot modulate its price, then what it essentially gets out of it, even with the reduced uncertainty, is it only gets $200,000 instead of $1 million.

Who captures the other value? Basically payers and patients capture the rest of the value in this story. So this really I think illustrates very clearly the impact of timing upon the implementation of a stratifying test in drug development. The price is nearly always set with novel drugs quite early in the drug's life, essentially immediately after registration or around registration.

This shows if one isn't able to adjust price, which is I think generally the case today, the company who is manufacturing this and who is disincented essentially from discovering and applying a stratifier, although the total value for society stays roughly the same, or perhaps increases with this reduction in certainty. So I think this is one very important factor to look at, is currently there are disincentives for pharma companies to do this sort of work post initial fixing of the price.

What about diagnostic companies? There certainly seems to be some incentives for diagnostic companies to do this sort of work. If you think about the potential diagnostics, if they were able to capture the rest of this value, then there would be very big incentives for them to do this work, because they'd be able to charge money for the test.

However, current reimbursement schemes for diagnostics do not reward for value creation. They are essentially technical reimbursement schemes, and this supply is around the world. This isn't just the United States which has this situation. So there are I think insufficient incentives in many cases for diagnostic companies to invest in this, particularly when we look at the attrition equation which I showed you earlier on.

If you are going to invest in predictive markers and you're trying to look at hundreds of potential medicines, which ones do you invest in, and how do you deal with the attrition of all of those

projects which never get to market? So this, again, underlines the fact that there are really not all that many incentives in place for diagnostic companies to do this work in a systematic way, and this is essentially because of the loss of value which comes out of this, because they are not able to get reimbursement based on the value that they create.

So as I say, the capturing of the value depends on pricing and reimbursement conditions, obviously intellectual property plays a role, competition, and timing plays a role.

So the key messages out of this are the value capture of a linked diagnostic/therapeutic depends on many factors, including pricing, reimbursement, intellectual property, competitive market conditions, and the specific characteristics of diagnostic and therapeutic.

Along with the scientific and clinical considerations, whether, when, and how this value was created, we believe is inextricably related to who captures it. So unless you have a stronger correlation of value capture and value creation, those disincentives will remain. Our view is that it would be wise to encourage value-based flexible pricing in reimbursement systems to provide a level playing field that together with intellectual property protection appropriately rewards diagnostic and therapeutic innovation.

This is a summary of those points. I don't think I have to go through it in any great detail, because I think I've teased out the main points already.

I just want to acknowledge a number of colleagues within Roche. Lou Garrison has cooperated with this in terms of putting this model together, from the University of Washington, and to some colleagues at Genentech and Boston Consulting Group as well. Thank you very much for your attention.

DR. WINN-DEEN: Thanks very much, Tom.

We're going to go right into our next talk, which I think follows nicely on this. We're going to hear a little bit more about economic challenges of integrating pharmacogenomics into clinical practice.

Kathryn Phillips joins us from UCSF, where she is a Professor of Health Economics and Health Services Research in the Department of Clinical Pharmacy. We have heard from her colleague, Dr. Veenstra, in the past. I hope this will be a continuation of our education on basically the health economics of working in this area.

DR. PHILLIPS: Good morning. I appreciate the opportunity to be here today, and I know that I'm the only speaker between you and lunch. So I will keep that in mind. I won't be cruel.

We all know that there has been a lot of hype concerning pharmacogenomics. Some people are saying it's going to revolutionize our lives, but where are we now with pharmacogenomics? Some people would say it's here, you'd better get on the bus or you're going to get run over. But others would say well, where are the benefits? Where's the beef? I don't see anything good coming from this. I realize it's cruel to put a hamburger on the slide at this point, but hopefully economics can help us figure it out.

So today I'm going to go over some of the economic challenges of integrating pharmacogenomics in clinical care, I'm going to go over some of the steps needed to maximize the value of pharmacogenomics and how economics can help us do that, and I'm going to go over three case studies. If you read the newspaper this morning, you know that there is even more news regarding these.

So why is economics even relevant? Well, it provides both a toolbox and tools. The toolbox is a conceptual framework, and the tools are the methods that we bring to bear. Economics can be boiled down to two things. One is incentives. In other words, here we are interested in why is pharmacogenomics adopted or not? What type of incentives will maximize the value of pharmacogenomics?

The other critical piece of economics is value. And by here, I don't mean money only. What is the value of pharmacogenomics? How is value defined? How does value change by whose perspective we're looking at? And how can value be measured?

I think it was important to first tell you just briefly where I'm coming from, and that I do

wear three hats. I'm primarily an academician. I do research on the application of economics of pharmacogenomics, on drug safety and policy issues, but I also do some work with the government which has helped me understand their view.

I work with the FDA, Steve Gutman in particular, advising them on pharmacogenomics, and I'm a member of EGAPP, which I understand the committee is already familiar with. I also do some work for industry, which has helped me understand their side of things in terms of how they define what value is.

So today I'm going to cover three steps. First of all, that we need to understand the importance of economic and non-economic incentives. We need to consider value from multiple perspectives, and we need to use innovative approaches to address new paradigms.

I'm going to use three case studies which you're probably familiar with. Herceptin, Iressa, and CYP 450 drug-metabolizing enzymes. First point, understanding the importance of economic and non-economic incentives. Pharmacogenomics adoption will only occur if there are properly structured, aligned, and built in incentives. I often hear, and I heard this morning, that physicians need to be trained, when economists would immediately jump up and down and say no, that is never going to be enough, there need to be built-in incentives for physicians to use pharmacogenomics, or it will never occur.

The problem is that incentives push in different directions, and the incentives for adoption may vary based on the characteristics of the intervention. Here is a laundry list of some characteristics that provide incentives for adoption. This is my own list.

In life threatening versus a chronic condition, if there is a strong advocacy group or industry interest, obviously there are high reimbursement coverage and rates, and I understand the committee has already talked about reimbursement. As my colleague was just saying, if pharmacogenomics is used early in the pipeline as opposed to later, if it is used for immediate versus future treatment decisions, if it is

used for focused, narrow treatment decisions.

A very important one that I've been hearing a lot about is that if pharmacogenomics can be used for off label indications, there is a lot more interest in using it. If it's used for ongoing monitoring versus one-time use, if it targets an acquired versus an inherited mutation, when it dictates what treatment will be used as opposed to suggest the treatment or dosage, and then finally one that you might not have thought of, which is pharmacogenomics is more likely to be implemented when it is not considered pharmacogenomics.

In other words, we frequently call it personalized medicine, targeted therapy, smart drugs. Now, why might that be the case? Well, first of all, the concept of personalized medicine is much bigger than pharmacogenomics. For example, it includes use of family history. So it builds on existing approaches, instead of appearing to emerge de novo.

It is easier for people to understand and support the concept of personalized medicine versus genetic testing. One reason being because it emphasizes the drug as opposed to the person.

Let's look at some case studies. Herceptin. This illustrates a very fast and successful adoption. It is one of the best known examples, although people don't consider it to be true pharmacogenomics because it targets a tumor. It has proved that targeting to small populations can be feasible and profitable for industry. Sales keep increasing, they're going to go up today probably based on the newspaper articles.

In 2004, sales were $479 million, a 70 percent increase in one quarter alone. It's important to note that testing here is for gatekeeping, not for dosage decisions. In other words, if you test positive, you get the drug.

Iressa is an example of a fast but currently unsuccessful adoption. Here we have a case where the FDA accelerated approval of the drug, but the drug has been essentially withdrawn from the

market because post approval clinical trials showed no significant survival benefit. However, the drug does appear to benefit specific populations, but until recently there has been no diagnostic.

There is one now developed. We marked it by Genzyme, but right at the moment there is limited availability. It is an expensive test, and right now it is unknown what the benefits will be.

CYP 450 testing illustrates slow adoption. There have been many implementation challenges, the multifactorial nature of drug response, the lack of data linking mutations and clinical outcomes, variability not only across drug classes, but within drug classes as well. In this case, testing is of the person, and that raises more ethical issues. Testing here at the moment is not a strict gatekeeper test. In other words, the incremental benefit of the test is harder to measure.

The second point. Consider value from multiple perspectives. All stakeholders want evidence of value, but they're going to differ in terms of their perspectives. Unfortunately from a societal perspective, there is very little documentation yet of the value of pharmacogenomics. We did a review of all the studies to date, and we only found 11 cost effectiveness analyses of pharmacogenomic interventions. A very limited range of conditions have been studied, and the results were quite mixed.

What are some of the challenges to determining the value of pharmacogenomics? Well, first of all, differences in perspective. In the value, determinations are often made before the product reaches a clinical setting.

I was talking to Fay about my talk before I came, and she said you're talking a lot about the pipeline before you get to the clinic. I said, but that's because the economic decisions are often made long, long before the product reaches the clinical setting. Therefore, we need to consider economic incentives throughout the pipeline, and evaluations need to be conducted before the intervention reaches the clinical setting if the societal benefit is to be maximized.

There are a number of technical issues in determining value. Lack of data I've already

mentioned, linking pharmacogenetics to outcomes, comparative effects on therapeutics, and on the products themselves, because much of the data are proprietary, so that economists like me can't get our hands on it.

We have to evaluate complex, multifactorial conditions. By definition, diagnostic drug combinations are more complex to analyze than the separate interventions.

There are a number of policy and political issues. There are few incentives to assess the economic from a societal perspective. We don't see those incentives for advocates, industries, FDA, CMS, insurers. That's not usually their role. Pharmacogenomics often has the benefit of preventing what has not occurred. It is always harder to measure the value of prevention. For example, avoiding adverse effects. It's very hard to measure what the true value of that is.

Also, with diagnostics. They often are harder to measure the value of. I often hear people say, well, the up front testing cost is going to outweigh the downstream savings.

Herceptin illustrates a successful adoption, despite the lack of documentation of societal benefit, and I'm going to pause on this slide because this is a very important slide. Many people do not realize this. Herceptin is expensive. In the newspaper today it says it's actually $4,000 a month. It increases median survival by a few months.

There have been a few economic analyses. One was done by a group at Harvard and was considered to be well done. They concluded that Herceptin cost $125,000 per quality-adjusted life year gained. The important thing to understand about that is that anything that's over around $50,000 is usually considered we're not so sure if the benefits are worth the cost, and outside of the United States, approval of the drug for national formularies was slow because of the concerns about the cost.

Iressa. Now, Iressa illustrates how failed adoption has the potential to create large, societal losses. Sometimes we don't think about that, in that a withdrawal of the drug from the market incurs large losses not just to industry, but to society as well because of the patients who don't benefit, the

regulators having to spend all that time regulating, and in general it increases public concern about drug safety.

CYP 450 testing is an example of where widespread testing could have a huge economic and societal impact, but it is going to require some creative and complex approaches to assessing the value.

We did a study back in 2001 that found that there was a linkage between adverse drug reactions in P450 mutations, that was a first step. We more recently did a study just looking at CYP 2D6, and we found that it could have a large impact because many drugs are metabolized by CYP 2D6, that testing could be relevant to 189 million prescriptions, and $12.8 billion in expenditures annually in the United States, particularly in the area of mental health and hard to seize drugs.

But, and this is a very big but, there is currently insufficient data to assess the impact of CYP 2D6 testing. There is very limited data on the clinical outcomes of testing, and Strattera mentioned the availability of the test.

My third and final point, use innovative approaches to address new paradigms. We have already talked this morning about the role of diagnostics, co-developed diagnostics, and drugs that are going to play an increasingly important role. As we know, that requires integration of historically divided industries and regulatory mechanisms, and it requires early consideration of diagnostics, which we just heard from my colleague.

I am doing a study for the FDA looking at barriers in the diagnostic pipeline where I'm interviewing a lot of key leaders. I have heard three major barriers mentioned. One is money, both in terms of initial investment, biomarkers, and then reimbursement rates.

The second is availability of data in samples, and the third is the clinical utility of tests are often not evaluated, and thus it is difficult to demonstrate the value of diagnostics.

With Herceptin and Iressa, we have seen that it will be challenging to develop and

determine the most appropriate diagnostic. With Herceptin, several tests were approved, but there is still debate over which test to use, and the development of diagnostics is often going to require multiple stakeholders who traditionally have not merged forces, academia industry and the FDA.

With CYP 450 testing, it illustrates it will be challenging to adopt pharmacogenomics when it's relevant to multiple diseases and drugs, because P450 testing is only done once in your lifetime, but the results are relevant to multiple diseases, drugs, and clinical specialties. So it's unclear who is going to advocate for testing.

Another critical issue is whether the test will be considered diagnostic or for screening. For example, Medicare covers diagnostic tests, but they do not cover screening tests. In this case, it's a bit unclear which one the test really is.

So it's unclear whether consumers are going to seek this out. Providers will provide, industry will have incentives to continue to develop such tests, and whether insurers will cover these tests if they are considered screening.

So to summarize, some of the next steps to address economic challenges of integrating pharmacogenomics, understand the importance of economic and non-economic incentives, incentives do matter. They're often contradictory, but they can be shaped by health policies.

Consider value from multiple perspectives, the definitions of value will vary, but value must be determined one way or the other. If it is not done from a societal perspective, then it will be driven by other perspectives. Therefore, I would argue that we need incentives for more economic research.

Third, use innovative approaches to address new paradigms which require a truly multidisciplinary approach in innovative funding mechanisms. Unfortunately, social science often lags behind basic science in this area. Why is that? Well, it's a riskier area to do research in. It requires more in-depth understanding of basic and clinical science, and it's hard to get funding in this arena.

It also requires development of an evidence base. The Pharmacogenomics Research Network is a good example. They are developing a database, however they explicitly do not include issues regarding application of their technology.

Then EGAPP once again is a good example, but ultimately EGAPP will end, and those issues then will need to be institutionalized if those evaluations are going to continue.

So to conclude, pharmacogenomics is here now, and will keep coming. I believe that there will be an inevitable push towards pharmacogenomics because it's part of a larger trend towards personalized medicine.

For that, genetics information is only one piece, but it will be a critical piece. I believe the government, therefore, has a critical role in facilitating the appropriate use of pharmacogenomics in order to maximize its benefit by shaping incentives, by ensuring that value gets measured from a societal perspective, and by facilitating innovative approaches. Thank you.

DR. WINN-DEEN: I want to thank both of our speakers for this session for very informative and insightful presentations. We have got about 20 minutes for Q&A from the committee.

Muin has his hand up already, so we'll let him go first.

DR. KHOURY: I'd like to thank both of you this morning. I have learned quite a few tricks today. But it is very interesting that we are embarking on what we call personalized medicine.

We still have to have a societal perspective on this. I think as a public health professional, I really subscribe to this endeavor.

I wanted to ask both of you sort of a question around this pipeline, the incentives or disincentives, and maybe use a couple of examples. When things are out and we discover that they are suboptimal or have side effects, they tend to be withdrawn from the market.

For example, the COX2 inhibitors which are very effective, unfortunately they double or

triple your risk of heart disease. I don't know how much it translates into absolute risk with respect to patients.

In the area of vaccines, for example, and that's something you don't talk about, or we haven't heard about, a few years ago there was a rotavirus vaccine that was very effective. Unfortunately, a few percent, a few per million babies had intussusception, and as a result, the vaccine was pulled from the market.

We are talking about very rare side effects in some cases, which is the rotavirus vaccine. Although the benefits were really proven to save a lot of lives as far as diarrhea as a major global health threat, I guess around the world, much more than in the U.S.

In the case of the COX2 inhibitors, there were millions of people, and I'm one of them, sort of the back pain and other things depended on having a steady flow of that therapeutic.

So can you kind of revisit those two examples? I'd like both of you, because these were sort of distal to the pipeline. By then, I guess the drug is already on the market, the price has been set, but side effects emerged, and instead of studying why some patients are more susceptible to heart disease as a result of COX2 inhibitors, the drug was pulled from the market.

So there is a clear disincentive, economically at least, to study that. So help me out a little bit with that example.

DR. PHILLIPS: Well, that's very interesting. It speaks to the idea that some people think that pharmacogenomics is going to be a panacea. I'll return to the newspaper article this morning. Although I read it, my time is 4 a.m. in the morning, so I can't guarantee I read it correctly, but I thought it was very interesting that they mentioned Vioxx.

As far as I know, pharmacogenomics couldn't have helped that issue at all.

DR. KHOURY: But we need investment in developing biomarkers.

DR. PHILLIPS: Yes, yes.

DR. KHOURY: That's the question I'm asking is to find out why.

DR. PHILLIPS: But in this case, we don't know of anything that could have helped identify who was going to benefit and who was going to be harmed by Vioxx.

DR. KHOURY: Right. But it wasn't done before. Could it be done now retroactively I guess postmortem? Or is it too late to save those categories of drugs?

DR. PHILLIPS: Well, the other thing I thought was really interesting about the article, they never mentioned the word "pharmacogenomics." It was all grouped together in this idea about personalized medicine, and it was all portrayed as we can now cure cancer through personalized medicine.

So I get a little nervous when I see those types of messages going out to the public that are going to raise hopes that maybe it's going to take awhile to address.

MR. METCALFE: So just to maybe answer, I think the safety aspect of this, certainly Merck was highly incented to try to find a predictive marker. But I think it's probably, and I don't know enough about the specifics about it from the Merck perspective, but it is practically a very difficult thing to do, to reliably predict. So this is in terms of predicting, and not monitoring, to reliably predict who is likely to suffer an adverse event because of a drug when you're looking at something that happens in a very few percentage of cases, an extremely difficult thing to do.

It's not only difficult to find the predictive marker, but it's also difficult to validate it as well. You would require very big studies to validate that in order to demonstrate that effectively. So that's one thing.

The other thing is that in many of those cases, particularly in the Vioxx case, you still have a drug on the market which is an alternative, and obviously if you have one drug which has a higher frequency of safety issues than another, you are going to use the alternative which doesn't require the

predictive marker. I think that's very clear.

There are some cases, as with, for instance, the use of the TPMT test, where that is a safety marker, you're looking at something which is relatively frequent. Unfortunately with that marker or that test, you can reliably predict who is most at risk from safety.

So there are some exceptions to this rule. I think that it's going to be very difficult to do this from a safety perspective. Certainly in the rotavirus case you mentioned, if one had been able to do that, then perhaps there would be a case to do that. I think the manufacturers are also reasonably well incented to do that at the moment, if there was something which was feasible.

DR. WINN-DEEN: Kevin?

DR. FITZGERALD: I'd like to thank Muin for his question, because I want to piggyback right on top of that.

Before I do, I just wanted to mention one other thing. I'm fascinated by the fact that an economics researcher would see incentives for the need for more economics research.

(Laughter.)

DR. FITZGERALD: But in any case, what I'd like to ask you, both of you, the flip side of what Muin was asking. He kind of focused on the safety. I'd like to ask what the incentives, the economic struggles, and challenges might be on the efficacy side.

What is the possibility here for rehabilitation of drug products that have failed in a sense in the past because groups weren't identified necessarily that could be identified now that might benefit?

So BiDil of course would be the perfect example recently. Now my understanding is that also received new patent protection, so that obviously would help. So you'd have to probably distinguish between when that might be possible, and when that wouldn't be possible.

Another drug I'm thinking of as a possibility of an example, I don't know if you're

familiar with it, is Eflornithine, which of course originally was considered to be a cancer drug. It turned out to be one of the best treatments they found for Gambian sleeping sickness. Of course there's no market for that, but then it actually got onto the market as a facial hair remover.

(Laughter.)

DR. FITZGERALD: So it's these kinds of things, the beauty of it being of course now that it is back active, you can hopefully move some of that into Gambian sleeping sickness treatment. So I'm just wondering, what are the possibilities here to go back and look at different ways of rehabilitating old products?

MR. METCALFE: So I think you have a case where new insights would allow you to use an existing compound in a different indication. As long as there is sufficient patent protection, I think there is plenty of incentives to do that, and plenty of possibilities to do that.

I think from our point of view, the two biggest, or the area where the incentives are between what are out there at the moment and our view of what the societal perspective is are most misaligned, where you have a drug on the market already which is being successfully marketed where there is the potential for you say sharpening the target of that.

I think as I tried to lay out, there are few drug incentives for drug companies themselves to work on that. There are incentives for others to work on that, there are incentives of payer organizations to work on that, there are incentives to a certain degree for diagnostic companies to work on that, but there are few incentives for drug companies to work on that.

In general, I think the diagnostic industry doesn't have much incentive to invest heavily or speculatively in this area because it doesn't get value-based reimbursement. There are cases where there are companies now, diagnostic companies investing in let's say a test for improved prognosis of breast cancer, but that's because there are enormous general economic benefits from doing this.

I think that they are reasonably speculating that they will get a good economic return on this. But as soon as you go away from the biggest opportunities, the incentives for diagnostic companies decline quite rapidly.

As for the cases that you mentioned, I think each case has to be looked at on its merits, but we don't see that as being a massive misalignment between potential societal benefit, particularly with orphan drug legislation.

DR. PHILLIPS: I will agree that's what I have heard. I will add the related issue of off-label uses where my industry colleagues tell me that the business models coming out all really heavily emphasize off-label use, in which they expect to make their money off of off-label use.

The insurance people I talked to are shaking in their boots because they have a really hard time dealing with the reimbursement of off-label uses because they don't have any evidence base to deny coverage. So they are caught in this in-between of they don't want to ration care, but they don't have enough evidence on which to turn back these requests for reimbursement for off-label use.

When you're talking about these very expensive drugs, they see it as a really critical issue.

DR. WINN-DEEN: James?

DR. EVANS: Yes, one of the things that has puzzled me is the lack of lawsuits that have been brought against, for example, physicians who don't use TPMT. For example, most of my colleagues don't, and certainly lawsuits are kind of an incentive or disincentive obsession with physicians.

I was wondering, from your perspective, I didn't hear either of you mention issues of liability. It seems to me those might be important in bringing pharmacogenomics forward or not.

My other question is unrelated, and that came up in the survey results we saw earlier today. That is in those gray areas, and it is almost always going to be a gray area about whether a

pharmacogenomic test predicts that a certain person might respond better or might respond worse, do you think that insurers will tend to try to deny coverage for that drug for those individuals for which there is some evidence that they would not respond as well? So those two questions.

MR. METCALFE: So on the liability perspective, it is obviously I think a reality in the U.S. market. I think where you have a clear standard of care, and where that standard of care isn't adhered to, then there is obviously much more risk or chance, whatever way you look at it, of litigation.

I don't think we have a strong view of that, except that it makes sense to provide enough evidence to establish a clear standard of care where you have that evidence. So I think that covers the litigation issue from our perspective.

I'm sorry. The second question was?

DR. EVANS: Well, following up that first part, do you ever think there will be a disincentive among companies to even do such research because they really don't want to identify those in whom an adverse reaction might occur? Does that make any sense, or is that more of a conspiracy?

(Laughter.)

MR. METCALFE: I mean, certainly it's one of the things that one takes into account when you look at litigation risk in general when you look at opportunities, but it's a reality which is out there, and I think that certainly we try very carefully.

Litigation I guess is the extreme end of the risk/benefit continuum, and we are very concerned about the risk/benefit continuum. We want to do as much benefit we can with as little risk as possible.

So you are going to shy away from the extreme ends of that and try and focus on where you are doing the most benefit with the least risk.

DR. EVANS: The second question.

MR. METCALFE: I remembered what your second question was.

DR. EVANS: Right. Do you think there is a chance that insurers would tend to deny coverage for drugs that were suggested that they would be less effective in an individual? Do you think that's a potential problem?

MR. METCALFE: I don't know whether it's a problem. I think it's a reality if you have clear evidence that a patient is highly unlikely to derive any benefit.

DR. EVANS: Right. I'm talking about what is going to be very common, which would be the less clear cut issue. So 60 percent chance of responding versus 30 percent chance of responding, which I think will be far more common with these tests than a really extremely clear cut.

MR. METCALFE: I think it's something that certainly we haven't debated this long and hard, so I don't think there's a clear cut answer.

One of the things that we look at carefully, though, let's take, and I think it is a good example that we've just seen which does inform us a little bit is the situation with Tarceva, where you have a patient, and there is no strong evidence base currently to deny patients, particularly Tarceva, based upon the EGFR expression rather than the EGFR mutation base.

If you are going to require patients to undergo a biopsy which is invasive which has potential mortality and morbidity in order to extract that test information, we think that's probably unreasonable to do that, lacking the strong evidence base, and even if the evidence base was there, that also might be questionable. So there are many questions which inform whether or not it makes sense to try and acquire the test information, and then the interpretation of it.

Obviously the clearer cut it is, the more likely I think it's going to be included in reimbursement decisions.

DR. PHILLIPS: I'll add very briefly that patients do play a huge role in determining

what pharmacogenomics interventions went forward. In the case of Herceptin, originally Genentech was reluctant to move forward. There was a huge patient advocacy move, patients chained themselves to the gates of Genentech and demanded the drug.

In that case, it did have an impact, but of course they were talking about breast cancer, and that's quite different than a lot of diseases where there are no advocates.

DR. WINN-DEEN: So I'd just like sort of a wrap up question for this morning's session to ask you both.

You did really a very nice job of helping us understand the financial decisionmaking and value proposition, thinking that a corporation goes through as it is making decisions about how to take things forward.

It is our charter to advise Health and Human Services. Do you have some specific things that you feel should be done at the HHS level that would benefit the industry in general? Advice, comments, anything? I'd just really like to give you a chance to make any pitches that you might have for government partnership in this.

DR. PHILLIPS: Well, of course I have to say economic research.

(Laughter.)

DR. WINN-DEEN: Okay, okay. Besides funding your grants.

DR. PHILLIPS: More economic research. I did try to cover that in my final slides, and I do think the government has an important role here, certainly in terms of the evidence base and helping facilitate the evidence base, and ensuring that value gets measured, that the perspective does get included. Otherwise, that might fall through the cracks.

MR. METCALFE: I think there are three or four things that we see. One is working on basically getting a clear regulatory framework and a clear set of standards. I think you've heard a little bit

about some of that this morning. Companies can invest with confidence in some of the opportunities around this because there is a clear framework out there. That's one thing.

The second thing is in general, and I think that we're seeing a movement in this direction, more funding for translational research. Happily, we're glad to see there is a movement in this direction. But I think it's slower than it could be.

The third thing I think is clearly having the right incentives aligned for profit-oriented companies in this arena. The particular area we see there is value-based reimbursement. Kathryn quite rightly says that one has to understand who is getting which value, and to try and have a clear interpretation of what the value is.

But if there is a clear misalignment of the incentives of the value correlation, it is unlikely that profit-oriented organizations are going to invest in these areas.

DR. WINN-DEEN: I'd like to thank both of you very much for your participation. I know that you came a great distance to be with us today, and we really appreciate your time.

We're going to take a lunch break now, and we will resume the afternoon session promptly at 1:15.

(Whereupon, at 12:20 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)

AFTERNOON SESSION (1:20 p.m.)

DR. WINN-DEEN: I'd like to ask the committee to take their seats, please, so we can start the afternoon session.

This afternoon we're pleased to have another committee alumni with us. Wylie Burke is going to talk to us about ELSI issues. Particularly she's going to focus on the issue of race and genetics as it pertains to differential drug response.

She is currently a professor and chair of the Department of Medical History and Ethics at the University of Washington, and is a faculty member in the Public Health Genetics Program and in the Medical Genetics Training Program.

I think basically she needs little more introduction to most of us, so thank you for joining us, Wylie, and we look forward to hearing your presentation.

DR. BURKE: Thanks very much. I really appreciate the opportunity to be here, although I must say that this topic has had questions that are difficult ones. So my main goal is to try and convey to you what I think is the complexity in these issues when we start talking about race, genetics, and differential drug response.

We can start with the complexity of race. Race is a term that's used generally to identify or at least it's assumed to identify groups with shared ancestry. That's the way in which we use the term, and implicit in that use of the term is a strong belief, particularly I think in U.S. uses of the term "race," that race has a lot to do with genetics. So there tends to be a tight alliance between those two terms.

I want to talk about the complexity and why we need to think I think more in depth about that. It's currently understood to refer to five groups. African, European, Asian, Native American, and Oceanic. But as we think about the use of race and what we mean by race, I think it's extremely important to understand that the definition of racial groups has changed over time.

A conspicuous example in the U.S. has been a relatively recent allocation of people from

the Indian subcontinent to Asia where they previously were not, and it has been used differently in different parts of the world.

In addition, when we look at countries like ours where there is a strong tendency to categorize people by race, in fact social factors are what determine what race you put down on your census form. So I think we have to be cautious about how the term "race" is used, and really a variety of different meanings that might be incorporated in the term "race."

Now, that said, there certainly is a relationship, though I would argue it's an indirect relationship, between race and pharmacogenomics. Self-reported race is correlated imperfectly, but correlated in a rough way with genetic measures of geographic ancestry. So researchers who have made efforts to identify highly variable markers that are particularly useful in identifying ancestry of the five major groups that I just referred to have developed marker panels that can be used for what is called ancestry testing. There is a rough correlation.

As a result, we do see some genetic differences, and they are generally differences in prevalence. So what we see is when we categorize people by race, or allow them to categorize themselves by race, we see that the prevalence of many gene variants, by no means all, but many vary with geographic ancestry, and therefore this indirect fashion with self-reported race, that of course includes variants that are associated with drug response.

So I want to give you an example of that. The CYP 2C9 which is one of the 450 genes, has been identified to have many variants, or several variants that are associated with reduced dose requirements for warfarin, the drug that's most commonly used for anticoagulation or blood thinning.

My colleague, David Veenstra, collated together a whole bunch of studies, and you can see the results here, that if you looked to people that were of European ancestry, the prevalence of variants associated with reduced dose requirements looked to be about 36 percent with a fairly wide range, but an

average of 36 percent, whereas in African groups, it was 8 percent, Asian, 4 percent, and I have put the figure at 10 percent for Native American, but you'll note that it's just two studies. Both done in Canada. One where there was a zero prevalence of these variants, and one where there was a 20 percent prevalence, so we shouldn't generalize too much.

The other point I would make here is that the preponderance of studies is of people of European decent, and the majority of studies occurred in North America. What that means is that most of our data comes from just a small slice of the world's population. I think it's fair to say that we know relatively little about the distribution of these variants around the world.

But CYP 2C variants are associated with a clinically significant drug response. So people that have these particular variants not only require lower doses of blood coagulation, but have a higher likelihood of having bleeding complications. There at least have been some proposals that this may be a clinically important genetic trait.

What's interesting about it is that the one racial difference that has entered into sort of rules of thumb in clinical medicine is one that's not explained by CYP 2C9 variants. So there is a kind of clinical wisdom among people who do anticoagulation therapy that Asian patients tend to require lower doses.

If you go to the Physicians' Desk Reference, the drug labeling, you'll find this paragraph. The highlighting is mine, because I thought some of these sentences were particularly interesting. So they start by saying, "Asian patients may require lower initiation and maintenance doses of warfarin." They go on to cite their basis, and it's one non-controlled study of 151 Chinese outpatients, and they go on to show the lower dose requirements.

So I think we'll note, uncontrolled study, small numbers, and in fact it is not a broadly representative population of Asians. It's actually one ethnicity within a large number of ethnicities that are

categorized as Asian.

These patients were stabilized on warfarin for various indications, so there might be a variety of clinical differences that also are important, and patient age was the most important determinant of warfarin requirement that's a known fact about warfarin.

So it's a rule of thumb that made it to the drug label. So there's enough conviction in the clinical world that this is clinically meaningful. I have certainly had docs who prescribed a lot of warfarin tell me that they believe this is the truth, but the evidence base for it is not particularly strong.

In fact, there are many, many sources of individual variability in P450 expression, of which the CYP 2C9 drug is one. This is a slide adapted from a study that was just summarizing all the many factors that might influence someone's response to a drug, and as you'll see, most of them are non-genetic or distantly related to genetic factors.

So many environmental or lifestyle factors might influence how one's P450 is expressed, or genes in that family are expressed, and therefore how one might have differential drug response.

Now, it turns out that a subsequent study on a different gene actually provides evidence about a possible genetic contributor to this apparent Asian requirement for a lower dose of warfarin. That's a study published recently by my colleagues from the University of Washington that was looking at the association between warfarin dose and VKORC1 variant haplotypes.

They were able to identify, looking at haplotypes, two groups. Group A, which was a group of haplotypes that were associated low dose requirements, and then Group B, another set of variant haplotypes that were associated with higher dose requirements.

The evidence is on this slide. When they looked at all the patients in their sample, and they actually repeated this in two samples of patients at University of Washington and Washington University, you can see the correlation between what kind of haplotype someone had, and what their dose

requirements were.

They also were able to take advantage of the fact that some of their patients also had the CYP 2C9 variants that were associated with lower dose requirements, and you can see the mutual effect of the two genetic factors in reducing dose requirements for VKORC1 for warfarin.

What is really interesting is that there does seem to be difference in prevalence between racial groups of these different VKORC1 variant haplotypes. Now, these data, the European, African, and Asian samples that were used to look at prevalence, were taken from the Coryell Data Repository.

What we have is that in Europeans, there is just under 40 percent who have that low dose haplotype, but close to 60 percent who have the high dose haplotype. With Africans, you can see that fewer of the haplotypes within the African population are explained by this Group A and Group B, but it's a different distribution. And then most interestingly, the Asian sample has a very high proportion of the VKORC1 haplotypes that are associated with low dose.

So this could be a genetic explanation for that clinical observation. Again, I want to note that the Asian samples were predominantly Chinese, so we continue mostly to know about this particular genetic issue in Chinese individuals.

This study also estimated the variants in drug response that could be explained by the CYP 2C9 and by the VKORC1 variants. Here is another important point. We certainly don't want to say we now know everything about why Asians might have lower dose requirements than other racial groups, because VKORC1 is only explaining 25 percent of the variants, and CYP 2C9 is explaining an additional 10 percent.

It is very likely that there are other factors, well, this tells us there are definitely other factors, and those other factors may be genetic, or they may be non-genetic. I think it's important to say at this point that either is a possibility. We await more evidence to understand this better.

I think there are a few issues here. One is that even on the genetic side, granting that both genetic and non-genetic factors contribute to drug response, even on the genetic side we're going to see complexity. So if you just looked at CYP 2C9, you got only a small slice of the story. If you just looked at VKORC1, you might get a slightly bigger slice, but it's still only a slice of the story, and there may well be other genes yet to come.

There are many genes that are involved in the metabolic processes by which the body responds to ingested warfarin. In fact, there was recently a study from Europe that identified variants in the APOe gene as having an effect on warfarin metabolism. Just one study. It comes from a group that has been doing lots of very good quality epidemiologic studies looking at APOe and its association with Alzheimer's disease.

It's the very same allele, that one that is associated with increased risk of Alzheimer's seems also to be associated with lower dose requirements for warfarin. We may well have others yet to come.

There are many exactly as you would expect, many well established non-genetic factors that are associated with warfarin response. I have listed the ones that seem particularly important in terms of clinical writing on this. The emphasis on nutritional status, GI disease has to do with the fact that one's Vitamin K level is very strongly influenced by the status of bacterial colonization.

So clearly the response to warfarin is complex. We are beginning to understand genetic contributors. They are very enlightening. They potentially will lead to important pharmacogenetic tests that will help us to prevent bleeding complications, and not surprisingly, we see some difference in distribution of the low dose variants across racial groups. But whether we are getting beyond race I think is not clear at this point. Hopefully I would argue, we are.

I want to get back to the point that races are genetically heterogeneous. Does it matter

that all we know about VKORC1 so far is in Chinese individuals by and large? I think the answer is yes, we should care about that a lot. In fact, as I showed you with the CYP 2C9 data, most of our data comes from Europe and the U.S., and most of it is on people of European ancestry.

We're seeing an increasing amount of research going on in Asia, particularly in China and Japan, so we're going to see some more data from that sector. But there are a lot of areas where we are just at this point very limited in the data that we have.

One collection of data that I'm showing you on this slide shows why it is going to be important to do very broad sampling. This was a study that looked at the prevalence of APOe epsilon 4 allele in populations around the world. The fundamental point I want to make here is that if you look at three different populations in Africa, you find a range from 9 percent to 41 percent, five different populations in Europe, a range from 5 to 31 percent, and so on.

The only population where they didn't see that broad a distribution seems to be in the three populations that were of Oceanic origin. The point here is that we can't just take a sample of people that have four grandparents of a certain geographic ancestry and believe that we have sampled that geographic ancestry. Within racial groups, I think it makes sense to anticipate, and these data support the notion that we should anticipate a lot of heterogeneity, another reason to be very careful about generalizations.

In addition to that kind of heterogeneity, and most of the studies that I just showed you were taken in situ, that is in the different geographic locations, we know that race and geographic ancestry in this country are related but not congruent. I'm just getting back to that point, and I just want to show you a few data points that were cited by Mike Bamshad in a very useful recent JAMA article on this point.

West African, most African Americans, at least most African Americans that came here as a result of the slave trade, or whose ancestors came for that reason, were originally from East Africa. If

you look at geographic ancestry testing panels in African American individuals, you find that West African markers account for about 80 percent of the ancestry on average, but the range is from 20 percent to 100 percent.

If you look at people who are self-identified as European, a substantial proportion of them have less than 90 percent European ancestry. That mixture is even higher and more variable amongst people who identify themselves as Hispanic. Bamshad cites data that people of Asian and African ancestry in other developed parts of the country tend to have more heterogeneous geographic ancestry than we see in the U.S.

Of course the other point I would make is this is a snapshot in time, in an increasingly global village, where there are many movements of populations. I read an article recently that said that immigrants from Africa who have come from Africa voluntarily now outnumber the population that is derived from people who came to this country from Africa involuntarily. Many of those people come from different parts of Africa than West Africa.

So we have, for example, in Seattle a large immigrant population from Eretria, Somalia, and Ethiopia, and given that heterogeneity, that we may see across people of African decent, we may see additional genetic complexity in the population self-identified as of African decent.

So we get to a fundamental question. Is race clinically important in drug treatment? Well, race clearly captures many potential group differences, as I've said. Even if you account for heterogeneity, and you always have to have that heterogeneity in your mind, we do see broad differences when we group people by race. Not always, but sometimes in issues of diet, issues of housing, issues of occupation, and issues of environmental exposure.

There has been a lot of work done, for example, looking at the higher risk that African Americans experience to be in substandard housing, or to be exposed to medically significant environmental

exposures, and as I've shown, we also do see a difference in prevalence of gene variants.

So it's not unreasonable to expect that we might see differences in drug response when you consider that all of these factors might influence how groups respond, or how individuals within groups respond to drugs. I think the question really is if we make such observations, what do we do with those?

The story of the VKORC1 and basically our growing understanding of warfarin's response says that it is worth investigating, and sometimes we'll find a specific genetic difference that may offer some explanation for a group difference. When we do, that genetic explanation will help us to identify individuals and move beyond the group.

So we can now envision a day where it matters what CYP 2C9 genotype you have, and what VKORC1 genotype you have, not what race you are, in determining your warfarin response. Other times it seems very likely that an observation of group difference will get us to an extremely important non-genetic difference that may be an important thing to address clinically.

In a recent editorial in Nature Biotechnology, the editorialist described race as "Simply a poor proxy for the environmental and genetic causes of disease or drug response." Now, crude markers can sometimes be very useful indicators to get us to questions that are important to research.

I think at this point it's very uncertain whether in the long run race is going to have sufficient predictive value to assist in drug treatment.

What are the implications of these kinds of observations for pharmacogenomic research? Well, clearly if we want to identify all the variants that are relevant to a particular drug response, we've got to study diverse populations in large numbers, because we run a real chance of missing important variants if we don't.

We need, as we do so, as we identify individual variants, to always have in mind that multiple genetic, social, and environmental factors are going to be important. So any one observation has to

be sorted out for its place within that mix, and obviously gene/gene and gene/environment interactions are going to be likely in that setting.

I think also the issue of orphan genotypes from a point of view of ethics and policy is an extremely important one to think about. Rarer genotypes that predict drug response are likely just by their nature of being rare to be less studied, and could be neglected, particularly in terms of the information we heard earlier today about the use of genomic information and drug development, there would be a real possibility that people with rarer genotypes could miss out.

Given the preponderance of research occurring in the U.S., the preponderance of drug development occurring in the U.S., I think we have to worry about a particular category of orphan genotypes. These are genotypes that aren't necessarily rare, but are genotypes that occur predominantly in minority populations. So they are not rare worldwide, but they are rare within the U.S. population, or relatively rare.

The issue of loss of lactase leading to the condition called lactose intolerance represents a very interesting example of this. A group of researchers wrote an interesting article in 1999 in the Journal of the National Medical Association claiming racial bias in federal nutrition policy.

Their argument went as follows. That federal nutrition policy has, for a long time, recommended milk product intake as a very important source of calcium in the diet. But as this group points out, the inability to digest lactose, that is to tolerate milk products, and in fact the rate of GI symptoms when one tries is quite high in virtually all racial groups except Europeans.

I'm not sure there is data on Oceanic groups, so I should give that caveat. But amongst Africans, Asians, Hispanic Americans, and Native Americans, it is a very common problem. Milk is not a good source of calcium for people who have this problem.

Now, again, it's a prevalence difference, so estimates of lactose intolerance amongst African Americans run something like 70 percent versus something like 15 percent in Europeans. As we

have been saying about other things, it is certainly not a simple racial trait.

So, for example, if you live amongst Europeans, lactose intolerance is much more common amongst people of Southern European decent than it is of Northern European decent. But what we have is we have basically something akin to an orphan genotype here, because we have policy having been made and billed upon the needs of a dominant group in the population who happen to have a genetic predisposition that is quite unusual worldwide.

I think it's a very important point that illustrates how careful we have to be about the orphan genotype issue.

I have said that one of the implications of thinking about race, genetics, and pharmacogenetics is that we need to do research in diverse populations. As we do so, we have a very important ethical concern to overcome. That is the existence of mistrust about genetics generally, and perhaps more specifically, about genetic research among minority populations.

I pulled out a couple of examples, but there are many examples. There is currently a lot of tribal mistrust in North America related to research misconduct in the past, or alleged research misconduct. So there have been examples where tribes have agreed to the collection of genetic samples for certain purposes. The most famous example is that of the Havasupai Tribe in the Grand Canyon who were very interested in the genetics of diabetes being investigated, because that was an important health issue in their group.

Then 10, 15 years later, a member of the tribe comes to a research presentation and discovers that the very same samples that were collected for that purpose had been used for ancestry, for migration studies, for studies of inbreeding, for studies of schizophrenia, for a variety of purposes that the tribe did not endorse and was in fact quite concerned that that research was done. That's one of many examples.

The other example is one of many examples. We do have data that suggests at least that there may be more mistrust and more worry about the misuse of genetic information amongst minority populations. Now, this is a study, the one I'm quoting, which is a survey of minority premedical students, had only minority students in the sample, so we don't have a comparative statistic. I would have liked in the survey data that we heard earlier to have seen a breakdown by race, because I think that would have been informative.

But certainly there is the worry there that discrimination has occurred on other bases, and this might be yet another basis for discrimination. So if we say that it's important in order for all groups to derive benefit from pharmacogenetic research in order not to miss the orphan genotypes that are really important, then this becomes a tremendously important imperative, to figure out how to develop partnerships, how to incorporate minority communities within the research enterprise to move forward together so that the research is done in ways that minority populations endorse and feel are good for their community so that they have assurance that the information will come back to them in ways that can be helpful.

I'm just going to end by talking about in summary what I think are the significant risks that derive from the use of race and genetics and the study of differential drug response, and then I'll make just a couple of remarks about how I think these issues apply more generally to ethical concerns in pharmacogenetics.

I have already made the point that we have inadequate research in minority populations, or if you want to put it in a global scale, we have too much research in the U.S. and Europe, and not enough in other parts of the world where the populations that are minority in this country are not minority.

We need very careful attention to the size and the sampling methods that are used for populations. We need to get away from the situation where we talk about Asian, but what we really mean is Chinese. We need, as we do that, to figure out effective ways to partner and address community concerns

and have community concerns be incorporated within the research enterprise, and obviously fundamental obligations of research integrity must be maintained.

If people give permission for samples to be used in one way, they really can't be used in another way. That's fairly straightforward.

As we go forward of course we also have to think about multiracial groups. Now, there is no simple bright line between where Africa leaves off and Europe starts. One of the interesting things about ancestry testing is that it tends to focus on clear examples. But we have many parts of the world where it's not clear, where there is a lot of what ancestry testing researchers call admixture. But really what is the inevitable heterogeneity that comes from trying to draw bright lines and saying here is one group on one side and here is another group on the other side.

In many parts of the world, this is an important issue. In addition, we have an increasing number of people in this country and in many other countries who very consciously identify themselves as multiracial. Just as we need to be concerned not to leave orphan genotypes behind, we need to think in terms of an increasingly multiracial society.

Clearly a very important issue is to avoid the notion of genetic reductionism in drug response, the need to recognize that even when we find genetic predictors that help us to identify people that may have higher or lower likelihoods of either adverse effects or effective responses to a drug, that that's only one of many contributors, and we shouldn't inflate it beyond what it is.

We need to be particularly mindful as we go into pharmacogenetics and do the job we need to do of bringing in lots of people from lots of different populations that we categorize in racial terms because that's how we're used to doing it, to make sure that we're avoiding the error of misrepresenting race as a genetic entity.

We need to recognize that racial group differences may have many causes, but most

importantly from the genetics perspective, genetic variation within racial groups is common.

Let me just step back and say if we think about pharmacogenetics from an ethics and policy perspective, what are the concerns? Well, I think one of them is that we've got lots of hypotheses of benefit, but relatively few examples where we actually have outcome data.

I think the CYP 2C9/VKORC1 example is very powerful. I would welcome research that would investigate the question of how much a panel that measured for those variants could assist clinicians in reducing bleeding complications of warfarin, and perhaps given that some of those variants are for high dose, getting people quicker to effective, therapeutic doses.

But I think the question has to be researched. We need outcome data. The hypotheses is great, it's very powerful. I'm sure at least some of these hypotheses will work out, but our experience for medical research is that not all good hypotheses actually turn out the way we think they're going to. So we need to think about that.

I think we need to be very careful about defining and protecting against risks. One of the risks is of ancillary information. I mentioned that APOe4 has now been identified at least on one study as possibly a contributor. So you can imagine in that imaginary panel that you might put APOe into the panel, and it might possibly improve your ability to predict who is going to have bleeding complications.

On the other hand, you're also going to find that information about Alzheimer's disease risk that people may not want to have. That may be a more significant risk that outweighs the benefit that might be provided. So I think we have to think very carefully about that.

I think we have to think about the risks of the paradigm, the risks of oversimplifying the predictiveness of the genetic information and thinking that it's simple. The TPMT example that Jim Evans mentioned did undergo FDA review in context of a drug labeling issue. One of the concerns that came up in the committee that considered that was not the issue that TPMT homozygotes would benefit from being

identified and given lower doses of chemotherapy that is dangerous for them, it is whether we would undertreat heterozygotes. So I think we have to look very carefully at those issues.

As with any health care intervention, try and be as global as we can about anticipating potential issues, and then evaluating them.

Then finally I would say that there is a fundamental ethics and policy concern that goes across the board in health care. It certainly goes across the board as we're talking about genetic innovations. That is as we find these wonderful new ways that we think will help to personalize and improve the quality of health care, can we be sure that everybody who could benefit from them will get them? I think that's a fundamental ethical concern.

I do want to give special thanks to my colleagues, Malia Fullerton, Ken Thummel, Susanne Haga, Karen Edwards, David Veenstra, and Julia Crouch, who is the coordinator of our Center for Genomics and Health Care Quality at the University of Washington, and our pharmacogenetics working group. Thanks.

DR. WINN-DEEN: Thank you very much, Wylie.

On our schedule now we have a little bit of time for discussion of ELSI issues. We'll let Wylie sit in the hot seat without the benefit of fellow panel members. So be kind.

But I think we identified a fairly long list of ELSI issues, and I don't want to necessarily confine our discussion of ELSI issues to the narrow topic that Wylie brought up if we have other things that we'd like to bring up. I'm sure she may have some comments on a variety of issues as well that could inform our discussion.

Are there questions? Kevin?

DR. FITZGERALD: Again, Wylie, thanks very much for your presentation and the issues that you raised.

I'd just like to expand upon one. You talk about our need to be careful with our sort of genetic reductionism or our geneticization of the issue. I'm also wondering, in your experience with these various groups, there is also, I might argue, the risk of a geneticization or a medicalization of risk and benefit overall.

So when you mentioned risks and benefits, you did tend to kind of be medical, but that's, I'm presuming, just because of the examples that you gave. I was wondering if you could speak more about just that whole idea of defining risk, period, as a group.

DR. BURKE: I think the point is well taken. Actually, and I agree completely with it, I think with pharmacogenetics, we are dealing in a more narrow area usually because we're talking about someone that has a health problem for whom we're considering a drug treatment.

On the other hand, if we got to a point where there was some genetic trait that allegedly identified people who felt themselves to be perfectly healthy who somehow now needed a drug, we definitely would have to look very carefully at the issue of medicalization. That goes more broadly across genetic risk information.

MS. BERRY: Julio?

DR. LICINIO: It was a really wonderful presentation. I had a question related to the issue of like mixed populations. Here, in the states, for example, people think very much like are you African American or Asian. You mentioned a little bit about people who consider themselves of mixed ancestry.

But in places like Hawaii or Brazil, where I'm from, those concepts are very different. People really are a true admixture of several countries. There are countries like parts of Malaysia or even India, et cetera. There is this kind of clear concept. It is even kind of almost non-existent.

How can this type of approach, like medicine that's given for hypertension in blacks here

in the states, how is it going to be used, for example, in Brazil or in Cuba? Should people take it or not take it? What do you think of this same issue in a culture in which the concept of race is very different from what it is here?

DR. BURKE: I think it's a very good point. What we can say, and I think most of my remarks are very specific to how we think about things in the U.S.

I think the fundamental answer is the same. Your point speaks to the extraordinary importance of making sure that research occurs in other populations, and that we don't exclude populations like Brazilian populations or Hawaiian populations where there may be less clarity about these racial categories that we're used to thinking about.

In fact, really the movement should be in the other direction, drop away from these racial categories that will have increasingly less use and less utility, and just do good population sampling to look for the variants that are relevant, or other factors, non-genetic, that are relevant.

DR. WINN-DEEN: Muin?

DR. KHOURY: Thank you, Wylie.

As always, I learn a few things from you every time. I was expecting to hear about BiDil, but I guess that didn't happen in your particular presentation.

As we think about sort of public health issues around pharmacogenomics, you being at the previous committees, I mean, you sat where these guys used to sit, trying to give advice to HHS agencies here.

I'd like you to for the next two minutes put that hat on and sort of help Emily and the group sort of think through the kind of recommendations to HHS. Some of them were already in your slides.

I want you to take BiDil first, because it is such a hot topic, and I'd like to see how it fits in the contract that you presented this afternoon.

DR. BURKE: Well, BiDil is a very interesting example. BiDil, from my point of view, has nothing to do with either pharmacogenetics or differential race response. So let me just start by saying that, and that's why it didn't show up as an example in my slides.

Let me explain why I have that view. The components of BiDil, isosorbide and hydralazine, have been known to be effective in congestive heart failure, which is the indication that BiDil is being promoted on, have been known to be effective in congestive heart failure since at least the mid-1980s. The first systematic study of those two drugs in congestive heart failure was published in the mid-1980s called the VHAFT1 trial. It was a VA trial.

It was predominantly a white population. There were some minority participants. It resulted in a 36 percent reduction in mortality for people who got that drug combination, compared to people who did not. So I don't think there's any question that the components of BiDil work in people other than African Americans.

The story of how it came to be proposed as something that might be marketed as a drug for African Americans, I think it's an interesting story. Jonathan Kahn has written a lot about it, and I think it has more to do with the regulatory procedures and the laws around getting patents for combination drugs than it has to do with anything specific to race.

But the one other trial I'll comment upon is the AHAFT trial. What happened was the researchers who were involved in the VHAFT1 and then a subsequent VHAFT2 trial, both of which showed effect of this drug combination in predominantly white populations, actually asked for a patent. There is a special kind of patent that I think is called the methods patent, but I will stand corrected by the FDA folks.

This is a patent that allowed them to create a combination drug even though the two drugs would still be available generically. That was denied. It was only after that denial that a subsequent reanalysis of VHAFT1 led to the suggestion that there might be a greater response to isosorbide hydralazine

amongst African American participants in VHAFT1 as opposed to European American participants.

Now, the study was not designed or powered to answer that question, it was merely a hypothesis, and I think it remains a hypothesis.

What was done then was the AHAFT trial. The AHAFT trial enrolled only African Americans, so it did not address the question of whether there is a differential response. What it did do, which I think is very helpful, was it showed that the combination of isosorbide and hydralazine remains an effective therapy. This is for folks with congestive heart failure that are on standard therapy. The question is whether an additive of hydralazine and isosorbide adds additional benefit. The AHAFT trial said it did, a 43 percent reduction in mortality. So it was a very striking benefit. I think that's helpful.

The trial was only African Americans, but I don't see that those trial results say that it only works in African Americans. We have prior data that says that European Americans benefit. I think we have a long history of testing drugs in one group, and then extrapolating those results to other groups. Most conspicuously perhaps testing men, and then saying women will benefit.

I actually think the AHAFT trial is a wonderful demonstration that this particular drug combination has value and may benefit some congestive heart failure patients. I don't see it as evidence that only African Americans will benefit.

Let me make one more comment while I'm on the BiDil story. That is that BiDil is a very expensive drug. The two components of BiDil remain available as generics. The price differential is something like $400 a month versus $60 a month. So I don't, speaking from the perspective of underserved patients, I don't see BiDil as being a breakthrough.

I do think the evidence that isosorbide and hydralazine are helpful is useful, and that physicians can use that information when they think about the patient on standard therapy who may need something additional. So that's my comment on BiDil. I'd be happy to answer more questions on that.

Getting back to the other point that Muin raised, what can HHS do? Well, I think the HHS perspective starts with the research perspective. I would say the tremendously important thing here is thinking very carefully about inclusionary approaches, about making sure that broad selection of populations is done. I think there is an argument perhaps for trying to encourage studies outside of the U.S., and clearly all of the ethical concerns that go along with approaching communities that haven't been involved in research and that may have some mistrust. I would say that's a leading issue.

From more of the clinical integration side, I think there is also a research piece. That is how do we fund outcome studies? How do we do post market studies after a drug has become available to look carefully at whether the drug is delivering on the promise that we said it was doing.

Then I think finally there's an HHS imperative to think about access. In the newspaper article that was referred to this morning regarding Herceptin, they had a price tag, something like $42,000 a year. It made me wonder whether patients in this country who are underinsured or uninsured get Herceptin when they need it. So I think those are policy issues that are important.

DR. WINN-DEEN: Joseph?

DR. TELFAIR: Thank you for your presentation. You have actually answered part of my question with your last set of comments.

But the other part of it that I think also would be really helpful is the understanding that in order to even get where you just suggested requires education, education both from the student level, all the way up.

So I was wondering, did you have any recommendations of how that might occur? You know, what I'm asking is that it's an infrastructure question really, and if you have any recommendations in that area, or any thoughts, I would appreciate it.

DR. BURKE: I'm not sure I have any thoughts that are going to be more specific than the

very important point that you just made. I think as we view this wave of genomics that's coming our way, we have to think very carefully about how can genetics be integrated into our expectations of school curriculum right from the beginning on up. So I think there is definitely a sort of public education curriculum issue that comes up.

I would highlight two other issues. We have to think carefully about how we're going to educate health providers. There has got to be a point of service. I get it when I need it, I don't get it when I don't need it because I'm not going to pay attention because I've got too many other things to do. So I think there really has to be a lot of thought as to what models are really going to work to help health care providers.

Then finally I think we have a need for education about what research is and why it matters, and what assurances we can give to the public that we will do research in appropriately respectful and appropriate ways, because there is a lot of research that needs to be done, and probably the most important resource in that research effort is the human participants that are willing to be part of it.

DR. TELFAIR: I appreciate that because that's your information. One of the other things I guess I was also getting at when I was thinking of infrastructure is that those who make decisions on how information gets disseminated, it goes and makes decisions on even how you structure the research process. In other words, make decisions about what populations to study, why to study them, and give information on that.

Because, as you know, many of us who do research tailor a lot of how we approach or even write the grants based on the guidance we get, and the guidance itself comes from, well, you know the process.

So I was wondering if you had any thoughts about education, not necessarily about just the public or even providers, but those who are in the process of having to make decisions about what do we

focus on. Even in training of the health care profession, and this is something that was in the Institute of Medicine report on public health, and I know this is kind of outside of what you are talking about, but it to me structurally fits.

How do you begin to even get those kind of steps of decisions, who are responsible for the public health care infrastructure or workforce to begin to think about this? What kinds of things would they need to know? That is what I think is what is important to us as well.

DR. BURKE: Yes, I would just say I think you're making very important points, and I think there are important issues that I'm not quite sure the best way to deal with.

Following the point you're making, it seems that one of the issues is how do you convene leadership in different, for example, NIH institutes to think very carefully about how to help the public in the best possible, most efficient manner? I can only say it seems to me those are tremendously important things.

DR. TELFAIR: Thank you, ma'am.

DR. WINN-DEEN: Other questions for Dr. Burke while we've got her at our beck and call?

(No response.)

DR. WINN-DEEN: Thank you very much.

DR. BURKE: Thanks for the opportunity to speak with you.

DR. WINN-DEEN: What I'd like to do now is actually ask people to turn to Tab 5 of their books, because we don't have slides, and I think it actually is useful to just look this over a little bit.

At Tab 5, we have a couple of things that we had identified. One was a list of key issues as summed up the basis of discussion at the June meeting. What follows that is then a proposal for an outline of a potential SACGHS report on pharmacogenomics.

I'd like to have a little bit of committee feedback on whether this is something that if you

look at the scope of this potential report, it is a report that's going to be a nontrivial task to write, even with some help.

So I would like to know before we ask the staff to start such a thing, that this would be something that we feel would be useful. I'd particularly like to hear not just from the committee, but also from some of the ex officios about whether it would be useful to you in your own organizations to have some kind of internally written HHS report on sort of the state of the state right now in terms of what pharmacogenomics is and what are the issues, and what are various agencies doing about it already? Where are we in good shape, and then of course our task is always to identify places where we want to make recommendations primarily about where we see gaps, although I think it is useful for us to also commend good work when we see it and point out to the Secretary not just the things that are going wrong, but also the things that we feel are going right within the organization.

So are there any comments? I know this is a very extensive outline, and we could go through it line by line, but I'd like to get just some sense of whether the group as a whole feels there is value in going through the effort of doing a report.

DR. LICINIO: I have a couple of specific comments, but you don't want them right now, right? You just want to get the general idea of whether we should do this?

DR. WINN-DEEN: What I'd like to do is if we think it's a generally good idea, then we should go through and make some specific comments about things that are either missing or need more work, particularly if there are areas that we could highlight where we think we might want to make a recommendation, even if we haven't totally formulated that recommendation. It would be I think helpful to staff to know that this is a point where we want to say something, and then the task force can go back and do some work.

DR. LICINIO: I think it's a wonderful idea, and I think it's particularly relevant. Because

what I have, and I may be wrong, but I don't think I am, within agencies, let's say within NIH, for example, there are institutes like NIGMS and people like Rochelle Long who are very supportive.

There are other institutes who don't see it as a big priority. It is like very uneven. So even within specific agencies, there is like, you know, some people think it's very valuable, and others don't think and it should maybe be investing in something else and not even understanding it very well.

So I think that to give like kind of a department wide like recommendation, or like at least kind of a consensus or review I think would be very useful.

DR. WINN-DEEN: Alan?

DR. GUTTMACHER: So I'm not sure that it will level the playing field of the NIH exactly. If anybody has any ways of doing that in general, I'd love to hear about them. But I do think, speaking for the NIH, first of all, I think it generally looks very good.

Second of all, I think it's useful simply as a summary of where things stand and where they ought to be, and third of all, I think the idea of including some specific recommendations to the Secretary is also useful. So generally it looks great. Yes, it would be useful to us as an agency, and specific recommendations from the Secretary would also be helpful.

DR. WINN-DEEN: Any other agencies that have pros or cons that they'd like to chime in on?

DR. KHOURY: I don't have any pros and cons, but I think as we think about pharmacogenomics and sort of the public health implications of that, it is very important to cover the whole spectrum from the bench to the trench, as somebody said yesterday.

When I think about CDC and some of the other public health agencies, you know, drugs, pharmacology in general, drugs in general don't have really a public health home in the sense that diseases have, like infectious outbreaks and things like that.

Drugs, medical errors, and drug adverse effects. I mean, with the exception of adverse immunization events, because immunization is sort of a public health activity, but drugs have a much more far reaching implication as far as the health of populations and access issues and some of the ELSI things that we heard from Wylie.

So I would hope the committee will sort of take the whole landscape from the NIH research agenda in how to incorporate pharmacogenomics with the right kind of research, all the way to the integration of evidence, a la EGAPP and some of the other processes, to cover some of the FDA issues. Then on the services side, HRSA.

So just look at the whole department. I basically don't see where, you've summarized what we all do. I don't see it here, and maybe I'm missing a page. Do we have some kind of a table that says what the feds are currently doing?

DR. SHAMANSKI: We're working on that.

DR. WINN-DEEN: There is, in Tab 5 behind the outline of the potential report, a one-page thing called Agency Feedback and Pharmacogenomics Policy Priorities. So this was the first level of feedback that we got.

We are still trying to put together a more comprehensive table, but this at least gives you some idea. It is pretty clear that the responding agencies are the ones that have the biggest stake here, but I don't want in any way to have the non-responding agencies unrepresented as we go forward. These are just the ones who chose to respond to our request for what is going on.

Go ahead.

DR. SHAMANSKI: I was just going to note that this first document was, as it says, the issues that the agency thought were most important. The subsequent work we're looking at is on the activities that are actually going on. So it's a slightly different focus of these two documents that we're

putting together. So the one that's in progress now is really focused on the activities. That's the one that we can use to look at gaps, overlap, and what is actually happening. This is more what we think should be happening.

DR. WINN-DEEN: Suzanne?

DR. FEETHAM: Speaking from the perspective of HRSA, I would reinforce what Muin was saying. I put it in the context as of yesterday where we really had the shift from the biological research to the broader context of the public's health.

I think, again, if this report can be done in that same way of looking at pharmacogenomics across all of these issues, the point of it is to inform where we need to go for the public's health. I think it will do the same kind of advantage of our discussion yesterday on the large population studies

Again, our focus is on the underserved populations. Every lens through here needs to be the basic point of access to care in all of these products.

DR. WINN-DEEN: So since we didn't do the Reed Tuckson table, we didn't get a chance to reiterate that there are certain overarching subjects, of which access is one, that inform and are important for basically all of these subtopics, so I think to your point, those things need to be considered throughout any document that we would consider writing.

So I'm going to ask then if people have any specific comments on the outline that they want to make now, and also to invite, if you don't have any specific comments because you really just need to think about it a little bit more, that you use Fay as a central conveyance point to send any additional thoughts you have after we leave here today.

James, and then Joseph.

DR. EVANS: One of the things I think is very important to have explicit in the report in

the outline is the issue of real demonstration in a prospective way of efficacy, whether you define that in purely medical terms, which is important, or also whether you include financial issues, which I think are important, too, as we heard today.

So, for example, under 2B, factors influencing uptake, I would think the very first thing there, if not as a separate subheading completely, but the very first thing should be demonstration of advocacy. It is what really will drive all of those other things, at least in the long term.

PARTICIPANT: (Inaudible.)

DR. EVANS: Well, in a way. But again, I think it should be highlighted much more importantly, and I think that under improved health status also would be outcomes with regard to financial issues, which would drive payers.

We just simply don't know if those things are going to pan out in the broad canvas, although we certainly hope they will.

DR. WINN-DEEN: Joseph?

DR. TELFAIR: Just on the side, I would agree with James on that issue. But on the other issue related to this, one of the things, and this is really not an area for me as everybody else's, but my concern has to do with we are going to put together a document that has recommendations to be able to tackle some of the bigger issues.

It seems to me that one big issue is, again, the infrastructure issue that I brought up a little bit earlier where you are taking on the topic providing some means by which a real good understanding of issues like admixture, a lot of things like the way that we think about the populations that are involved.

Something to the effect of what kind of regulations can be made that then allows us to best look at that population, research that population, or even look at ways that policy needs to be changed to better service that population. The focus would not be just on health care providers, but also decisionmakers

in the process.

DR. WINN-DEEN: So let me just ask you a clarifying question.

DR. TELFAIR: I know it's rambling.

DR. WINN-DEEN: No, no, it's not rambling at all. I think what I'd like to understand is currently there is some guidance when you set up a clinical trial that you should try and balance it by age and gender and sort of racial whatever that reflects the population you're planning to treat. Do you think we need to think about making some changes in the way FDA guides companies to set up that kind of diversity in a clinical trial situation? I'm just trying to get a little more granular on where you think we should be focusing that issue.

DR. TELFAIR: Well, I would say yes to that with the caveat that those who understand the functionality of clinical trials look at that recommendation closely.

I would suspect that given in ways that I have participated in recruitment and other things related to clinical trials, it seems to me that more attention needed to be paid to that aspect of it than what it usually does to begin to be able to focus a little bit more on how populations are selected, what gets population involvement, participation in clinical trials, you know, the kinds of more sort of basic, fundamental things that you do to achieve sample size, to achieve the integration, and those things that you are expected to have.

But I think those who are much more familiar with that should look at that. That's what I would recommend at a ground level, because that's what my involvement has been. But also in other research I would suggest the same thing, that also somehow or another there should be a criteria that requires that you look more closely at the population than just representation, not being a face representation, but another also representation of the population.

You can have, for example, African American groups that you're involved in, but you

know evidence is, like we just saw today, the heterogeneity within that group. Paying attention to that heterogeneity is something that you really should be paying attention to, which doesn't always happen. It should be something that I think also needs to be evidenced in any kind of application that you have, that you recognize that for what it is.

Not everyone does that. I think that was some uniform way that we can make a recommendation that that is done, yes, that's the direction that I'm kind of moving in.

DR. WINN-DEEN: Kevin was next.

DR. FITZGERALD: We can put this in the recommendations, too, because I think it addresses a variety of the points, particularly the ethical/legal/social area.

But from what we have heard yesterday and even this morning on the genetic discrimination survey, I think we could put in there that we'd begin public engagement now on this issue. Why wait? It doesn't have to be on the same size or scale as we're talking about the large population studies, because that's, you know, the impetus for that is a little bit different.

But still, I think some of the response to the survey data earlier today on genetic discrimination, people are saying this is the kind of data we want to have so we can put things into the bigger context. I think we could start on this, too, the same sort of thing.

Again, something that we don't have to necessarily look into, the Secretary can have someone look into. How should it start?

DR. WINN-DEEN: Right. I mean, it's not like we would lay that whole public engagement process out, but I think we can definitely get to a point where we say there needs to be a --

DR. FITZGERALD: Something has got to start now.

DR. WINN-DEEN: There needs to be a process, and whether it's related to, you know, sort of an early alert system from FDA that something is coming that might want to have an education of the

public component to it.

DR. FITZGERALD: Right. But I'm thinking even beyond that, what we've heard say with certain interactions with Native American groups, and other groups. Again, not necessarily groups that are categorized by even traditional sort of categories as "minority" or "racial," but start this broad public engagement now to even perhaps recognize for the first time that there are other sorts of delineations of which we are not yet aware that we wouldn't become aware of until of course we trip over them for some reason or another.

DR. WINN-DEEN: So you're talking about maybe not so much a pharmacogenomics thing, but an education on, you know, race is not race kind of thing?

DR. FITZGERALD: Again, it is pharmacogenomics in a sense, because again, what we're talking about, you keep listening to what our targets are. We are always talking about the public health and the benefits to the public health.

Well, what is public health except what the public thinks about it's health. I mean, why are we always dictating to the public what health is? I'm sure there were many of the researchers who were just shocked to find out that some small tribe in the Grand Canyon wasn't interested in finding out where they came from. I'm sure they were stunned to find that out. Who wouldn't want to know? Right? That's the kind of conceptual thing we can at least --

DR. WINN-DEEN: That's the difference between being an immigrant who wants to know where you came from and a native population who already knows where they came from.

DR. FITZGERALD: They want to know where we came from, right?

DR. WINN-DEEN: And why.

DR. FITZGERALD: And how do we get home?

DR. WINN-DEEN: Julio?

DR. LICINIO: There is an item at the last page about the issue of race what Wylie has just discussed. There is something that could be subsumed there, or it could also be its own separate issue, which is that if you study a group, like if you study a group because of its ethnic capacity and characteristics, in other words, if you recruit somebody not because they are hypertensive, but because they are hypertensive and Chinese, then NIH has been strongly recommended to do community consultation as well, and I think the issues of community engagement at least.

So I think that there could be like a subitem there, like community engagement just immediately after that one, because I think one would lead to the other. But just like studying people, like discussing the pros and cons of studying different groups without saying what you need to do once you study them, I think would be like a gap there.

DR. WINN-DEEN: Steve's making faces like he has something to say.

DR. GUTMAN: Yes, I do. I actually think this would be a fascinating report. It would be a panoply of activities, a mosaic that would be very hard to put together, but it would be a wonderful report.

I have no particular interest in any subject that would be in the report, but I have a great interest in if you were to step back and ask the question as you put this together and it plays off of what Alan said, getting different parts of NIH to be on the same wavelength is challenging. Certainly getting different parts of FDA is hard as we work with drugs and with biologics is challenging.

Of course getting FDA and CMS or FDA and CDC to work together becomes even more challenging. So I think it would be interesting to step back and actually ask. There's a lot of passion, there's probably not enough money, but there is a lot of intellectual capital being thrown at genomics probably in almost every nook and cranny of the Department.

The question I would have is is there some mechanism for better integrating,

synthesizing, or coordinating that activity, prioritizing that activity in making sure to define public health? It does seem to be aimed in the right direction.

As I recall, one of the swan song refrains from SACGT was this outrageous suggestion Reed put on the table. I believe it was Reed, that what the Department really needed was the equivalent to a drug czar for genetics. Maybe what the Department really needs is an equivalent, and maybe that's just delusional to think that's possible, but maybe it wouldn't be impossible to have a drug czar for pharmacogenomics to have someone at some higher level, at Mr. Leavitt's level, one of his deputies' level, who actually mapped out for the Department as a whole what it was doing, what it should be doing, where it was going. At least put that question somewhere.

Maybe it's just dumb. I mean, it's called truly impossible, or it is scientifically and financially unnecessary.

DR. WINN-DEEN: Well, you know, all suggestions are welcome at this point. I think what we'd like to do is probably, and I'm sort of speaking for staff at this point, but to try and ask the staff to go ahead and do some of the things that are outlined here.

We do have the offer of assistance, I forget which, yes. So we are not going to be doing this alone. So I'll recognize you in just one second. So I just want to make sure that we all think, just sort of nods of heads, that this is worth the task force continuing to work. We are interested in your feedback, please. Can you introduce yourself?

DR. RANDHAWA: Certainly. I'm sorry. I'm Gurvaneet Randhawa. I'm subbing for Francis Chesley. He's my colleague. This is a report which is pretty near and dear to my heart.

I wanted to just discuss two points that I think may be useful, at least from our perspective. One is as I was quickly leafing through the proposed outline, and I didn't really see the two that are nearest and dearest to our hearts, outcomes research.

DR. WINN-DEEN: We'll write those words down. No problem.

PARTICIPANT: DNA.

DR. RANDHAWA: DNA.

DR. WINN-DEEN: He's right, it's there.

DR. RANDHAWA: Just to expand on that for two issues. One is I heard additional demonstration of efficacy. The outcomes when you talk about efficacy are usually the outcomes you talk about in effectiveness.

That actually is the biggest area that our agency is concerned with. So to the extent that we can focus on not only identifying more outcomes that are useful, but also distinguishing the efficacy from the effectiveness outcomes.

The second part that I was hoping the report would highlight is trying to distinguish near-term initiatives from long-term initiatives. So when you're talking about launching new multidisciplinary research projects, I think they are rather long term.

We already have existing initiatives of ongoing collection. All that's required is linking them better and using better and hopefully uniform standards of collecting information so that the clinical outcomes in an HMO research network capture the same kind of data as another hospital or organization.

Those are thorny issues to sort out when we're doing outcomes research. So I was hoping that would be a point of emphasis in the report.

DR. WINN-DEEN: Well, I think for sure a point of emphasis in the report is to have agencies which fall under the HHS umbrella work as well as they can among themselves. It's a little more difficult for us to recommend to the Secretary working with external agencies, but we can certainly point out that there are significant external stakeholders that need to be engaged, that this is not just an HHS issue, that it has to involve the significant stakeholders that are out there, corporate and, you know, from the insurance

world, all the different ones.

Muin?

DR. KHOURY: Just to add to what Gurvaneet just said, and if you look at Section 3D, number 3, which is under surveillance mechanisms needed, this is sort of the presentation you kind of heard from Bob Davis a couple of meetings earlier.

Under 3A, you have effectiveness. Maybe what we should do, and we can help you with drafting the report, is add to surveillance mechanisms needed, surveillance and outcomes research infrastructure needed. Because as part of let's say HMO research, networks and other kinds of similar activities, that's where you distinguish effectiveness from efficacy, sort of real world utilization.

DR. WINN-DEEN: Right. I think it helps to say the word "efficacy" by itself, and to say "cost effectiveness," which I think is what I mean when we say effectiveness. Is that what we're talking about?

DR. KHOURY: Not necessarily. I mean, you can look at effectiveness in the real world in the absence of cost.

DR. WINN-DEEN: Right.

DR. KHOURY: We're all subscribing to the economic model here. But suppose something works in a randomized clinical trial, would it include people all of the same, you know, race, ethnicity? And then you throw it out in the real world where you have three people come in with other preexisting conditions, and the efficacy or you think the efficacy of that drug may not lead to the same effectiveness in the population.

DR. WINN-DEEN: Okay. So you are talking about the translation from a small trial population to the general population?

DR. KHOURY: Yes. I think that is what Gurvaneet is referring to.

DR. WINN-DEEN: So this is, again, one of those things that the staff is sitting here writing madly because you're going to have all these definitions so that we all know what we're talking about, much as we had to do in the coverage and reimbursement report so that we could agree on terminology.

Do I have other comments that people would like to make at this time?

(No response.)

DR. WINN-DEEN: Because if not, we will be having a task force meeting between now and the next, in fact, we'll probably have a couple task force meetings between now and the next full committee meeting. I think the next full committee meeting is not until February or something.

PARTICIPANT: March.

DR. WINN-DEEN: End of March. Oh, well, we've got time for five or six committee meetings. Anyway, I think there's a lot to do if we're going to go ahead and do this. It is very helpful to the committee and to the task force in particular to have the help of as many brains and hands as we can get to make this happen.

DR. KHOURY: Emily? Am I on the task force? I don't remember.

DR. SHAMANSKI: Yes.

PARTICIPANT: You'll remember when the report starts to get formed.

DR. WINN-DEEN: On the 15th version of the report that you have to read and comprehend.

I think there were some other general committee business, but I think as far as I'm concerned, we've sort of beat this horse to death at this point. So I yield the floor to our acting chair.

MS. BERRY: For the final blow?

DR. WINN-DEEN: Yes. She's probably going to have us read another red line or

something.

MS. BERRY: Okay. A 10-minute break.

(Recess.)

MS. BERRY: Let's finish up. What's up on the screen you don't have, we don't have. We're going to go through this together, though, and it's an attempt to summarize our deliberations and discussion over the past two days.

Of course the first issue that we tackled yesterday had to do with the large population research initiative resource. You can just take a brief moment or two to review. Does everybody have this now? Okay.

Just read it on the screen and see if that accurately summarizes yesterday's activities and the thinking for moving forward.

DR. FITZGERALD: In that first paragraph, sorry Sarah, back on the top paragraph, I understand that it could potentially fit under ethics, or even if one wants to talk methodologically, under scientific. But actually I think the public engagement panel could even be set up there separately. Because in a sense, it is something new. It has its own kind of methodology, it has its own sort of science to it. So we'd have scientific public engagement and ethics panels.

MS. BERRY: Joseph, did you have a comment?

DR. TELFAIR: I'm not sure what the first paragraph on the next page is going to say. But one of the things that we agreed to I think was that we would take into account the things that Kevin just mentioned by going back to the, if we could, go back to the reports, or presentations from those folks and include them in the conversation. I mean, in the deliberations.

If we need a subgroup or an ad hoc group, we'll be able to then take those recommendations and use those as part of the additional work of that task group. That's what we had agreed

to. I'm not sure if that is exactly reflected in that, but I'm just expanding a little bit more on what is said in that paragraph.

It wasn't if needed, it was just that was something we said we would do. It was more definitive than that.

MS. BERRY: Is everyone in agreement that we are going to produce some sort of work product, some sort of report to the Secretary on the large population research project resource initiative?

DR. TELFAIR: I thought we were yesterday.

MS. BERRY: Okay. So we're going to do that, and the task force that already exists is going to lead that charge, and it will include some additional outside members who will help in putting this together.

DR. TELFAIR: And the content, in addition to the additional content areas, will be those that are covered earlier around the research, ethics, and public engagement part.

MS. BERRY: The last item, the last paragraph here in this section, this goes to the request from NIH for a formal statement on our part with regard to the public engagement initiative. While not all of us were here at the bitter end, there was some discussion about whether that's within our purview, within our charge to do.

So it would be good to have everyone's input as to how far you think we should and can go. I think everybody felt that public engagement was critical and should proceed, but to what extent we can make a statement to that effect and to whom, I think that would be important to nail that down.

Kevin?

DR. FITZGERALD: I mean, I understand your concern, and I agree with it. So could we not interpret what Francis asked us as would we be against, or would we want to postpone or inhibit his looking into it for some reason now, before our report comes out.

We could just say no, we don't have to then have any charge or whatever in order to proactively tell them to do it, but we could certainly say that we responded in such a way to say we didn't see any problem with them going ahead and doing it, as far as interfering with anything we're trying to do. How's that?

MS. BERRY: Any other thoughts?

(No response.)

MS. BERRY: Sounds good.

DR. GUTTMACHER: My sense of it, again just sort of watching from across the Web, was it wasn't just efforts to engage support for the concept, it was to engage the public about its views of the concept. That is that the public, it's not a question of voting yes or no, but very much how the public thinks such a thing should be done, what kinds of questions it ought to be able to answer, what are the priorities, those kinds of things.

DR. FITZGERALD: Actually, that's right in the sense, too, that you don't presume their support.

DR. GUTTMACHER: Right.

DR. FITZGERALD: Right. Because they may not be.

DR. GUTTMACHER: And one would hope to find out what the opposition to it is.

MS. BERRY: Muin?

DR. KHOURY: I guess I have no comment on this paragraph. But if you all remember, a lot of the discussion was about having the public health sort of voice at the convening function, both from health departments and other stakeholders.

So you don't want to inhibit NIH to do what it wants to do, which is engage the public. But if you want the maximum bang for the buck, I think these efforts should start early on involving the

whole department.

I think that would be a good thing that would come out from this group, but you're not ready to say it now I guess until the final report. You don't want to inhibit Francis from doing what Francis does, but your recommendation will go out to the whole department.

MS. BERRY: Did you have a comment?

DR. HANS: I just was going to ask Sarah to get rid of the word "study" in the second bullet, just make it initiative or whatever it's going to be.

DR. KHOURY: Large population research initiative, LPRI.

MS. BERRY: Sylvia?

MS. AU: Maybe we should go back to Hunt's offer of doing that interim letter with the recommendation for the community consultations before the report comes out. The report's going to take awhile.

DR. KHOURY: But would you do it to advise NIH, or to advise HHS?

MS. AU: It would be advising the Secretary that HHS should, I think that was Hunt's offer. Well, Hunt's offer was to the NIH, but I'm sure that he would expand it to HHS. That would be a quicker document to come out than the report.

MS. BERRY: But are we ready to come up with recommendations in advance of completing the work?

MS. AU: I think it was just a letter supporting that discussions with the communities should begin as soon as possible. We're not telling them how to do it, we're not telling them who to ask. I think it was just that concept.

DR. EVANS: Would we need to do that?

DR. GUTTMACHER: Yes, I don't think we need that. I mean, you can believe we heard

you, we heard you. We agree, and that makes sense to us. We're going to do it, even.

MS. BERRY: Any other comments on this section? Does this adequately summarize what our deliberations and conclusions were?

(No response.)

MS. BERRY: All right. Let's move onto gene patents. There is, as we know, an upcoming NAS report. It is due I think November 9th if my memory serves me correctly. Debra graciously agreed to lead a group, and we already have some volunteers, and there may be more to follow, to review the report when it comes out and advise us if there are any issues that the report raises that we should consider.

DR. WINN-DEEN: Are we going to only send that report out to the subgroup? Or are we going to send that out to everyone for their reading pleasure?

MS. CARR: Everyone.

MS. BERRY: I think everyone will have it, but the subgroup gets the extra duty.

DR. WINN-DEEN: That's fine. I would like that clear so that everybody's expectations are the same.

MS. BERRY: Right.

DR. WINN-DEEN: Since I'm on the subgroup, I get it either way.

PARTICIPANT: May I ask the question, is Sarah going to buy a copy for everybody?

DR. SHAMANSKI: I've already been in touch with the committee, and we'll get copies.

PARTICIPANT: I was just going to clarify that it has been delayed to November 17th the last I knew.

MS. BERRY: Hot off the press. Any other items to discuss on that section on gene patents?

(No response.)

MS. BERRY: Okay. Coverage and reimbursement. Not much to discuss there. It just summarizes the fact that we had some edits that were approved today by the committee, and the report will be finalized and sent to the Secretary.

Genetic discrimination. The first item, this was Agnes' idea, right? Am I remembering correctly? To transmit the findings to the Secretary.

The second bullet deals with the fact that there were some questions that we had as a committee that we thought might be useful the next time that they conduct their surveys.

Joseph?

DR. TELFAIR: The audience was going to be also the public, as well as providers. I don't know if that needs to be clarified, but I think we would have questions for both audiences that they are looking at.

MS. BERRY: Right.

Kevin?

DR. FITZGERALD: Shouldn't we also mention that we get an update on the legislation H.R. -- I'm trying to find it here.

MS. BERRY: 1227.

DR. FITZGERALD: 1227, right. Just so that we put that down.

MS. CARR: In the letter to the Secretary, you mean?

DR. FITZGERALD: No, this is just our notes, right?

MS. CARR: Yes. These are actions, next steps.

DR. FITZGERALD: Okay. I'm sorry.

MS. BERRY: Does anybody have any action items pertaining to the legislation? And we can't really -- I mean, we're constrained. Anything to add to this section on genetic discrimination?

(No response.)

MS. BERRY: Pharmacogenomics, our last section. I'll give everyone a minute or two to look at those bullets. Is everyone in agreement that a comprehensive report along the lines similar to the outline that was presented in our briefing books will be prepared? The task force will lead the charge.

The goal will be to have a draft ready for our next meeting, either March or possibly in June. Any other additions to that?

(No response.)

MS. BERRY: Hearing none, it's a wrap. Our next meeting is March 27th and 28th, 2006. We don't know where it will be yet. Location to be determined.

MS. MASNY: Cindy, just a question about would we be looking at other issues for the next meeting, to discuss at the next meeting besides what we've listed there?

MS. BERRY: Yes. Do people have time?

MS. CARR: Does anyone have any suggestions? I do think if both of these topics, you know, we're ready to come back with them, I think that will take most of the two days.

You probably wanted to have something, hear something more about genetic discrimination again, and perhaps Cogent Research offered to come back. I think they're going to have some additional data in February that would be of interest to the committee, so we could consider that.

But if there's anything else that is also not on our priorities list, or you feel there's something that needs to come up, we're also, remember, going to have the patents Academy presentation and discussion of that.

Agnes, go ahead.

MS. MASNY: The only thing that I was thinking that came up a few times during our presentations over the past two days was the issue of law enforcement use of genetics.

In our original charter, that was one of the things that was presented as looking at some of the legal, social, and ethical issues related to forensics. Although we didn't have it as a priority area, I wonder especially in view of moving forward with recommendations on the large population research initiative, there were concerns that were expressed there, whether that's a topic that we should look at formally as a committee.

MS. CARR: Could I just remind the committee that the Department of Justice is an ex officio to the committee. The person who was appointed ex officio has left the agency, the department, and a new ex officio hasn't yet been appointed.

I guess, well, it is up to the committee obviously if you wanted to add that to the agenda. But it might make sense to wait until the Justice Department is back on board and confer with them and maybe have somebody from, at some point, maybe in March in next year, to have somebody from FBI come back.

MS. BERRY: And there is also legislation that's being considered, I know particularly over on the Senate side. I don't know what the House has done with it, pertaining to DNA sampling, genetic testing, and its use, both by the defendant and by the prosecution.

So if we have something like that on the agenda, it might be good to get a briefing from the Hill as well on the progress of that.

DR. FITZGERALD: Just a quick question for Sarah. Is there a limit to the appointment process? Or can Justice just keep delaying and not give us an ex officio representative? Is there like a time line or time limit they have to send someone our way?

MS. CARR: No, we would welcome them at the table at any time, of course. We have been checking.

DR. FITZGERALD: You have? Thanks.

MS. CARR: Yes, we do check in with them periodically. We'll do it again.

MS. BERRY: Any other comments?

(No response.)

MS. BERRY: Do we have a motion to adjourn?

PARTICIPANT: So moved.

PARTICIPANT: Second.

MS. BERRY: All right.

(Whereupon, at 3:24 p.m., the meeting was adjourned.)