# SECRETARY'S ADVISORY COMMITTEE

# ON GENETICS, HEALTH AND SOCIETY

## TENTH MEETING

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National Institutes of Health
Bethesda, Maryland

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I N D E X

I N D E X (Continued)

LARGE POPULATION STUDIES SESSION

P R O C E E D I N G S

**OPENING REMARKS**

DR. TUCKSON: Well, good morning, everybody. Do we have everybody out of the super duper breakfast room? I really want to thank all of you. I am sure that we could spend a lot of our time doing travel nightmare stories for yesterday and I'll just sort of say that when my cab sunk on the GW Parkway, I knew that this was going to be an interesting experience, and that was fun to paddle the cab out of the muck there.

I'm actually very happy that we are here at this facility and I really appreciate and I really hope that somebody will be able to transmit our appreciation to the NIH staff and team for allowing us to be here. It is very, very difficult to get a meeting at NIH nowadays and we really appreciate all the extra effort and security, the folks that come out, the dog sniffing guy standing by the van is always impressive. It always makes me want to come here.

(Laughter.)

But the problem is—I'm sort of giving you a segue for the next meeting—we're going to be out east hell somewhere—

(Laughter.)

--which is actually very nice, College Park, but we're going to be a long way from here. The problem is that we're not big enough for hotels to love us because we don't use enough rooms and so we—apparently, unless you have enough rooms they don't care about your staying in their ballroom or their meeting room so they're mean and we hate the hotel industry in Washington a whole lot.

(Laughter.)

And I'm very upset but—anyway, so we're going to be out in wonderful College Park, though, and I joke but it's a lovely place and we're happy that somebody wants us but anyway—so, with that, can you believe this is the tenth meeting of the Secretary's Advisory Committee on Genetics, Health and Society. I mean this has been a real effort and we've been around a good while now, and I think that that sort of is its own challenge is to ensure that we're making a difference. So being also the second committee—it's really our legacy is much longer than ten meetings and so we really do have the challenge of focusing in on making a difference, and I think that's the watch word for what we do today.

The public was made aware of this meeting through notices in the Federal Register as well as announcements on the SACGHS website and listserv. I want to welcome members of the public who are in attendance, as well as viewers tuning in to the web cast, and we thank you for your interest in our work and thank all of you who joined us.

Before we begin, I'd like to let you know that we have some new members and I want to do a warm welcome of them.

First, let me ask, Barbara, could you—Barbara Burns McGrath, could you just give us a one sentence of who you are and where you are, and welcome aboard? You have to push the button right there.

DR. McGRATH: There.

DR. TUCKSON: You got it.

DR. McGRATH: I just flew in from Seattle moments ago so I'm delighted to be here. I'm Barbara Burns McGrath from the University of Washington and I'm a nurse and a medical anthropologist.

DR. TUCKSON: Terrific. Well, we're very glad. And let me also introduce—allow her to introduce herself, Andrea Ferriera-Gonzalez if I said that right.

DR. FERRIERA-GONZALEZ: Actually you are really close.

(Laughter.)

DR. TUCKSON: Now this is a diplomat.

(Laughter.)

Somehow or another I have made an error and I don't feel bad about it.

DR. FERRIERA-GONZALEZ: Gonzalez will be fine to make your life easy. I'm Andrea Ferriera-Gonzalez. I'm a professor of pathology at Virginia Commonwealth University and also the Director of the Molecular Diagnostics Laboratory there. Thank you.

DR. TUCKSON: Thank you so much.

Also, let me welcome Steven—well, Steven, I'm going to let you say your name, too.

DR. TEUTSCH: After all the times we've been together.

DR. TUCKSON: I'm just trying to be cautious.

(Laughter.)

DR. TEUTSCH: I'm Steve Teutsch. I'm a medical epidemiologist at Merck, retired from CDC, and now I do a lot of work on evidence-based medicine and evidence-based public health.

DR. TUCKSON: I know that Steve is a good person and we have been around a lot together. So thanks for letting me have fun at your expense.

I want the new members of the committee to feel comfortable and I want you to feel at home. This is a complex committee and so we're going to do everything we can to try to give you a sense of catch up quick. I would urge you, though—and, unfortunately, I'm the kind of person who is shy and so—

(Laughter.)

--I tend not to ask very basic questions and be afraid that if it's a too basic a question for something I'm trying to catch on, and then I sit there and I'm completely lost for the next three years. So I would urge you to really just ask whatever you need to ask and catch up but we want this to be a comfortable and a fun experience for you.

To help make sure of that, let me just ask the other members of the committee if they would very briefly give a one sentence introduction of themselves so you'll know some of the people who are the actual members of the committee. I appreciate the ex officios, by the way, but I'm just going to do this fast for the members of the committee just to run around real quick.

DR. EVANS: I'm Jim Evans and I'm a medical geneticist at the University of North Carolina.

MS. AU: I'm Sylvia Au and I'm the State Genetics Coordinator in Hawaii.

DR. FITZGERALD: Kevin Fitzgerald. I'm at Georgetown University in the Department of Oncology and also the Center for Clinical Biologics.

DR. TELFAIR: I'm Joseph Telfair. I'm at the University of North Carolina, Greensboro, in Public Health.

MS. C. CHEN: I'm Chira Chen. I'm a patient advocate and I also work at University of California, San Francisco.

MS. MASNY: I'm Agnes Masny. I'm a nurse practitioner at the Fox Chase Cancer Center in Philadelphia, Pennsylvania.

DR. LICINIO: I am Julio Licinio and Chairman of the Department of Psychiatry at the University of Miami.

DR. LEONARD: Debra Leonard, Vice Chair of Laboratory Medicine at Cornell, Wilde-Cornell Medical College.

DR. WINN-DEEN: Emily Winn-Deen. I work for a molecular diagnostics company called Cepheid.

MS. CARR: We also have two other members, Cynthia Berry, who unfortunately has a flooded basement, but Cindy is a partner at Powell Goldstein in Washington, D.C., a law firm, and she's an attorney.

And then also Hunt Willard, Director of the Institute of Genome Sciences and Policy at Duke University couldn't be with us today but he has also been working very hard on one of the issues of the committee's, the draft report on large population studies. So he is a big contributor to the committee as well.

DR. TUCKSON: And just real quick on the ex officios, I want to start with Lieutenant Colonel Scott McLean. Is that right, Scott?

DR. McLEAN: Yes.

DR. TUCKSON: Please let us know where you are.

DR. McLEAN: I'm a clinical geneticist stationed in San Antonio and I represent the Department of Defense.

DR. TUCKSON: Terrific. Steve, do you want to go around and do you and the rest now?

DR. GUTMAN: I'm Steve Gutman. I'm with the FDA in the Office of In Vitro Diagnostics.

DR. COLLINS: Francis Collins, Director of the National Human Genome Research Institute here at NIH and I am the NIH liaison member.

DR. TUCKSON: Good.

DR. ROLLINS: Jim Rollins, one of the medical officers at CMS. I work for the Coverage and Analysis Group.

DR. CAROME: Michael Carome. I'm the Associate Director for Regulatory Affairs in the Office for Human Research Protections.

DR. TUCKSON: Great. And we have a new member. Denise?

DR. GEOLOT: Denise Geolot, Director of the Center for Quality at the Health Resources Services Administration.

DR. TUCKSON: Great. Did I miss any of the ex officios?

For the committee members again, the ex officios from the agencies are exceedingly important to us, especially as we—again the watch word for this meeting is "let's get stuff done." Let's move this ball forward. And the ex officios are absolutely essential to that and that's why I wanted to highlight them, and we appreciate everything that you all do for us.

Well, this is also a time of transition in the staff. The wonderful Fay Shamanski has gone to a new position at the American College of Pathologists. We would like to make sure, Sarah, that we thank her and that she gets a note that says that we mentioned her and we appreciate everything that she has done for us.

There's recruitment underway to fill the position. In the interim we're also benefiting from the wonderful services of a really special HHS program called the "Emerging Leader Interns Program." They're doing rotations with our staff. Dr. Kathryn Kolor, who is based at CDC in the Office of Genomics and Disease Prevention, has been working on the large pop studies draft report and public comments.

Kathy?

DR. : There she is.

DR. TUCKSON: Hey! Thank you.

And then we also are pleased that Dr. Joseph Malone, who is based at FDA in the Office of Policy and Planning, has been assisting with the pharmacogenomics draft recommendations.

Thank you, both, very much.

Well, since our last meeting in March, we received responses from the Secretary on the coverage and reimbursement report that is in your tab and essentially it indicates that he's obviously in receipt of it and that they are in the process of working through the recommendations. It pretty much is a very early statement of response and I don't have anything—there's nothing more definitive than that.

We also have a response on our letter on the incorporation of genetics, genomics and family history into the electronic health infrastructure. Both of those are in tab 3 of your briefing book.

We also just received a response to our letter on directed consumer marketing of genetic tests and a copy of this letter is located in your table folders. You'll be hearing more about that tomorrow.

Regarding the coverage and reimbursement report, I'm pleased to report that Cindy Berry and I met with the CMS administrator and their staff, and Mark McClellan, a couple of weeks ago on the

committee's recommendations. In particular, we focused on the five recommendations that are directed at the Medicare and Medicaid programs.

I will say that Dr. McClellan was having an extremely intense day that day. It was very clear that something extraordinarily important was going on. He made very great efforts to have not only himself but his senior leadership team in the room with us.

And I want to note, James, if you would pass to them that it was very much noted and appreciated the priority that Mark McClellan placed on our meeting. Despite whatever the challenges were at the moment, we had his undivided attention for as long as we needed it and they took our report very seriously.

Our recommendations specifically regarding the screening exclusion, billing and reimbursement of genetic counseling services, national versus local coverage decisions were of particular interest, and so he has assigned—he assigned out follow up work to the appropriate people on his staff, including his legal team and he assigned a coordinator, Mary Lacey Rather, as the point of contact to follow up so there's a clear way of process and going forward. So I think the committee, again back to our mantra of trying to move things along, that was a very important meeting for us and we are pleased about it so we will follow up.

Similarly, we have a meeting or I have a meeting tomorrow afternoon. I will have to break away from our conversation to meet with Elias Zerhouni tomorrow, the NIH Director, so I will have a chance. I love our staff and our team. Apparently I'm to memorize this briefing booklet here and do this meeting with Elias so I will be staying up tonight doing that but I'm actually looking forward to that and I think we have a lot of issues. Again, this is important because I think the Director of NIH is taking our work seriously and wants this time to sit down and go through some level of detail so I'm pretty pleased about that meeting and we will talk to you.

I think the key thing is to continue to maximize the visibility of our work not only within NIH, within HHS, both of those together, I think that's really the challenge.

For the new members of the committee, we've been always struggling with how do you make that happen, particularly at the level of the Secretary of Health, given all the things that are on his or her plate at the time. I think we're just going to keep pushing and being very, very aggressive about it.

Now if I could put the slide up.

(Slide.)

We have a very broad charter and mandate. Within that broad scope, our agenda has been guided by a strategic plan that we developed collectively through a systematic priority setting process in March of '04. At the beginning of each of our meetings, I always try to take a moment to review our priorities because I think the committee has to always be focused on what is our focus, what are our priorities, and where are we in implementing our strategic plan. It's easy to get lost in the woods and not keep a high level view of where we are.

So do you have the slide there? Oh, okay. I wasn't seeing anything. So she's got it all under control. They're so good.

First of all, we did a vision statement describing our priority issues and how we reached them. We did that in 2004 and for the most part it continues to reflect and guide our work as a committee. So the checkmark is there because, in fact, we have done that.

The second priority that we had was genetic discrimination. It's our highest priority issue and to date we have developed three letters, commissioned a legal analysis of the adequacy of current law, compiled a phone book sized document of public comments that the committee has very laboriously collected as we really pulled together a significant amount of comment from all the major stakeholders in this drama, both the public as well as industry, health plans, et cetera. So we've pulled together these comments to document public concerns about this issue in a compelling way and produced a ten minute DVD of public testimonies.

We produced a report and nine recommendations on coverage reimbursement of genetic tests and services, and so we have attended to that. By the way, the genetic discrimination, while we have a check on it, it is a—we have done what we were supposed—we have done a lot of stuff there. We are very proud of what we've done but that issue is still an ongoing issue for us and I want to make sure that by putting the checkmark there, I want to indicate that we have performed but this will always be a continuing drama.

The coverage and reimbursement recommendation—we produced a—it has nine recommendations and those we have sent forward to the appropriate—to the Secretary and, again, mentioning we've gone to CMS. It has been out in the public and the private sector health care world, and we will need to be attentive again towards making sure that we drive that forward.

Next is regarding education and training. We have written a resolution about the importance of genetics education and training of health professionals and how that can be enhanced. Again I think we need to be always thinking about what if anything is the next step on this, and you want to keep that sort of in your mind.

On direct to consumer we've written two letters on direct to consumer marketing of genetic tests. We are—at the last meeting we had a good report about the collegial interaction between FDA and FTC and how they are moving forward on that, and so we'll be monitoring that as we go forward.

On the issue of pharmacogenomics, this—then we also—so pharmacogenomics was another major priority. The next issue that we have, of course, is large population studies and then gene patents. These three are going to be discussed at this meeting and so you'll get a sense that we're going to be really drilling into these as well.

Today we will also be advancing further our issues on genetic discrimination, direct to consumer marketing and oversight.

The issues of access, public awareness and genetic exceptionalism transcend all the other issues and are integrated into our work. So just again for the newcomers to make sure you get a sense, genetic exceptionalism is one that we have sort of been struggling with from the very beginning in terms of how much of our efforts are this is genetics outside of everything else versus genetics being integrated across a broad panoply. So we sort of see that as woven in so there's probably not going to be much that we see right now as a discrete project like the other ones.

Public awareness and how do we educate the public about being prepared for the genetic revolution and all the things that come with that is something that we try also to think about it in context with other things but we haven't addressed that as a specific initiative as such and that's something that we need to keep in mind.

The access issue was very much connected to the coverage and reimbursement report, and that was really the first effort to sort of make sure that we looked at that, at the access issue, as an important kind of deal so genetic discrimination again being work that we're going to continue to focus on.

So, hopefully, this gives you a sense of where we sort of are in our strategic plan that was developed in 2004. I emphasize 2004. This is now 2006 and so at some point we made decide, and you will be the ones to decide, whether or not we need to make some shuffle in this and whether or not there's something that's not there that ought to be. Should we be giving more priority to something else, go back to things that we've done work in the past and push that forward? I want to just keep those things in the committee's mind and at some point maybe we will have a chance to revisit this and talk about it.

So giving you a sense of where we are: The agenda I'm going to through in a minute but actually we're going to actually jump into the meeting for a moment. We've got a presentation from Judy Yost who is going to give us an update on the Notice of Proposed Rule Making on a Genetics Specialty for the CLIA Program. The reason we're going to go to this first is Judy may well be called away back to CMS for something that she has to do in Baltimore.

Judy, by the way of travel stories, apparently got up at like 2:00 or 3:00 o'clock in the morning to

drive down from outside of Philly, I think it is, to get here for this presentation and so that's just commendable that she would give this committee that kind of respect to make sure that she was on time. So I'm going to give her the opportunity to make her presentation.

As I mentioned, she is the Director of the Division of Laboratories and Acute Care at CMS. She's here to provide an update on the status of the CMS plan to augment clinical laboratory improvement amendments or CLIA program with a genetic specialty, which has been in development for a number of years. Tab 5 provides some background on this issue as well as a timeline of developments related to the oversight of genetic tests, specifically with regard to both CLIA and FDA oversight.

CMS has worked closely with CDC in developing a genetics specialty proposal for the CLIA program and Dr. Joe Boone, Associate Director for Science in CDC's Division of Laboratory Systems, is joining us today by Phone.

Joe, are you there?

DR. B. CHEN: Hi. This is Bin Chen from CDC. Dr. Boone is delayed on his way back home so he cannot join this meeting today. I'm sitting in for him.

DR. TUCKSON: Okay. Well, thank you. And your name?

DR. B. CHEN: Bin Chen.

DR. TUCKSON: Okay. Thank you so much. With that, let me just thank Judy for the presentation and after Judy's presentation and a couple of questions for her, I'll come back and we'll restate the deck in terms of the order of events and what you can expect over the next two days.

Thank you, Judy.

**OVERSIGHT SESSION**

**UPDATE ON THE NOTICE OF PROPOSED RULE MAKING ON A GENETIC SPECIALTY FOR THE CLIA PROGRAM**

MS. YOST: Good morning, everyone. How is everybody on this dreary day?

(Slide.)

I want to thank the committee for the invitation to meet with you today and also for Sarah and her staff for accommodating my horrendous scheduling and allowing me to be here this morning.

Since it's early in the morning and I only have a short period of time, we're going to fast forward on this presentation and move to what would be, I believe, your slide 14. It's going to say "Current Status of Genetic Testing Under CLIA."

We're going to assume that you know everything there is to know about the current CLIA requirements that include quality control standards as well as requirements for analytic validity. It also includes quality assurance requirements, requirement standards for proficiency testing, personnel qualifications and responsibilities with the lab director having the overall responsibility, recordkeeping requirements, and labs are inspected biannually. So that's our starting point for this morning which, of course, heads you to the first bullet that says, "Genetic testing is already covered by CLIA regulations under those standards."

In addition, there are specific standards already in CLIA for cytogenetics. There are quality control requirements as well as personnel qualifications and responsibilities.

There is, however, no genetic or molecular testing specialty currently under the CLIA requirements. The tests that you may want to call genetic tests are currently dispersed throughout other laboratory specialties such as hematology, microbiology, immunology, chemistry, even blood banking, I guess, if you want to go to that extreme.

We did, however, make some changes based on CLIAC. The CLIAC is the Clinical Laboratory Improvement Advisory Committee. They had made a series of recommendations to the Department of Health and Human Services regarding CLIA changes for genetic testing and we were able to, when we published our final quality control regulations, incorporate some of those recommendations.

One is a unidirectional workflow for PCR testing, quality control for PCR testing. We enhanced

the confidentiality requirements in those regulations as well.

(Slide.)

Just as a little bit of history because you can't do anything without the background and history, there was a Department of Energy-NIH Task Force that published a report indicating that there should be enhanced oversight for genetic tests. That was in 1997.

In 1998, the CLIA Advisory Committee did make specific recommendations to the Department regarding what should be added to the CLIA requirements to cover genetic testing.

Then in 1999, your predecessor committee, the SACGT, made recommendations to support those CLIAC recommendations.

So in 2000, May of 2000, CDC published what's called a "Notice of Intent", NOI, and that really is like a predecessor to a proposed rule. It just says, "We're thinking about doing a rule and here's what it may contain." Essentially that that notice of intent included were all of the CLIAC recommendations as well as a comparison to what existing comparable requirements already were included in the current CLIA requirements.

That notice of intent did receive quite significant comments. Interestingly enough, however, the comments were very balanced. They landed on both sides of the fence on a total continuum from a position that said, "Well, maybe we already do cover genetic testing in CLIA so maybe we don't need to do anything" all the way to the other extreme, which was "very prescriptive, very detailed requirements belong in CLIA for genetic testing."

Based on that Notice of Intent, the CLIA Advisory Committee updated and revised their recommendations. I believe you have those recommendations as part of your package today in case you would like to look at them.

Currently, I am pleased to say that based on all those recommendations, we do have a notice of proposed rule making in CMS clearance at this time.

Now I'm sure you're looking at that timeframe and saying, okay, what have you been doing since 2001 till the present since there is, as you can see, a noticeable gap in time. You're probably wondering what we've been doing. Well, quite a bit actually. I think it's important that we owe—and we do owe you an explanation regarding that.

One of the things that was so difficult was the fact that those notice of intent comments were very mixed so it's awfully hard to write something when you have comments that kind of can go either way. It's kind of hard to frame and craft language that accommodates those comments. That was one issue.

In addition, some of the recommendations made by the CLIA Advisory Committee were actually outside the scope of authority of CLIA. So that also gave us problems in dealing with that. What, in fact, do you do when we don't have authority for certain areas? We don't have authority under CLIA to require, for example, informed consent. We don't have authority to cover clinical or utility or validity. So those were difficult issues that we also had to deal with.

In 2003, as you noticed from my previous slide, we published a final quality control regulation and that one was actually even later than this one. Unfortunately, we have requirements published back in 1992 that had been extended four times until 2003 and we felt we really needed to finish those first. That was the priority for the CLIA program.

Well, for those of you who don't realize, when you publish a regulation you're not done. That's the beginning. You've got to educate your surveyors. You've got to get that information out to the laboratories so they know what the standards are in order to be able to meet them. So CMS is the implementing agency for CLIA and thereby we had to train our surveyors and provide education to the public in order to meet those requirements, and then we could take up the regulation for genetic testing.

One other issue that also came to play here was the fact that again CMS does not have authority for clinical utility or validity. For that reason, there was kind of a hole in the process because, as you know, one of the more difficult or complex issues is how do you get a brand new test from the laboratory

or the garage or wherever it is invented out to the marketplace and ensure that the test, in fact, does what it says it does? So we were sort—there were a number of recommendations that had come forward from this committee and other groups regarding how that should take place and then CLIA would basically pick up the pace and take it forward into the analytical piece to ensure quality testing on a day-to-day basis.

Unfortunately, that part has never taken place and so it kind of left us with a difficult position of not knowing exactly where CLIA should start and end because there was this other responsibility that has not been done, not through anyone's fault but because there just wasn't the wherewithal to do so.

So there were a number of issues that did intercede, which obviously took quite a while to address and so finally we do have this regulation in clearance at CMS.

(Slide.)

Now nothing is ever simple and nothing comes without issues. So these are the kinds of things that we'll be asking you as a committee, your colleagues in the genetic testing community, and the clinical laboratory community to be addressing:

What, in fact, should the definition—because this is a proposed rule so we are looking for your comments, you are the experts in the field, we'd like to hear from you what should the scope of that definition be for a genetic test?

How shall we handle informed consent?

What about the clinical validity piece? Where does it fit? How does it fit?

Proficiency testing is an issue because you know there is not a plethora of genetic testing materials just laying around waiting to be—particularly for rare diseases—waiting to be used for PT. So how would you deal with that?

Also, personnel qualifications. We clearly do not want to disenfranchise anybody who is already in the field. So how do you create the balance to ensure quality testing but not put people out of their jobs?

And then the old faithful research labs that are currently doing what they call is research but they are reporting results back so they do belong under CLIA.

So you can see that there are a number of issues that we'll be looking to you for comments because when you comment to a proposed rule we have to consider each and every one of those before writing the final rule.

(Slide.)

We've had a lot of input, a lot of excellent input from all of you and from our own advisory committee. We had comments from the notice of intent. We reviewed different professional standards and guidelines and the crediting organizations' requirements. We talked to subject matter experts and, of course, the other federal agencies in order to come up with—and I do want to thank CDC since Bin is on the phone for their invaluable assistance in drafting this proposed rule. The reason that it's at CMS is that all the CLIA regulations are published through CMS.

(Slide.)

Just for those of you who are not familiar with regulatory terms, there are actually more than just standards when you do a proposed rule. There is the preamble because that's where you're going to hear what is the rationale for why we did or did not do something, and that's where we're going to include the questions to the public for comments.

Then there are the standards. They actually constitute the smallest part of a proposed rule.

And then we need to talk about the impact. What are the costs of meeting these new standards? What are the benefits that will balance out those new standards, as well as the information collection?

(Slide.)

So, okay, where do we go from here? The regulation is on the CMS regulation schedule. I cannot promise you once it's out of our division and into clearance—we're going to do our very best to

get it through the system but we cannot promise you a date at this point in time. It's just too early to tell. It has got to go through CDC, FDA and CMS and NIH clearance before it will see the light of day, and then be signed by the Secretary.

Once it's published, we'll probably have a 60 to 90 day comment period. We'll compile and synthesize those comments into a final regulation and ultimately then train our surveyors. Again, we'll be looking to you to help with those kinds of things with ideas for that as well as to develop any guidance and educational materials to facilitate laboratory compliance.

(Slide.)

And last but not least, if you're interested in any further information about CLIA, I encourage you to visit our website. It has got everything you ever wanted to know or needed to know about CLIA and I do thank you for your time. I'll be happy to take some questions. You can always e-mail me or call me. That's our office number.

DR. TUCKSON: Judy, thank you. Dr. Chen, did you have any comments that you wanted to make at all on this?

DR. B. CHEN: No, I think Judy provided all the details that I think are very helpful for this audience.

**Q&A**

DR. TUCKSON: Well, thank you.

Judy, let me just ask as a first question here—first of all, thank you for the presentation and we appreciate it.

So let's make sure that we've got it all straight. I think we're going to need—my question is going to wind up being a request for some supplementary material from your office.

At the end of the day there is a very important oversight regulatory function obviously by CLIA in monitoring the appropriateness of laboratory services in this special area that we are concerned about.

What you are describing is that there are—if you look at the overarching public goal of what ought to occur in the public's interest to give it confidence and assurance that appropriate monitoring of these laboratory tests is being done that there are some gaps. There are some things that exist that are very good. There are some things that are—there are some holes. There are some deficiencies. You're describing then a process, if I understand you, by which those deficiencies are now being addressed in a methodical and logical way, and that you're saying that we, as a committee, may well want to follow progress there and maybe even have some input and maybe ask for the opportunity to comment here and there on some of these things as they go forward.

The first question would be timescale again. Is there an expected date by which there should be a conclusion to this stage of the process?

MS. YOST: Again, I can't commit to any date because I can't promise anything but, if all the stars align and everything comes together, we could possibly see something early in 2007 calendar year but again that's—there are a lot of places it has to go--

DR. TUCKSON: Sure.

MS. YOST: --after it leaves our office.

DR. TUCKSON: And so just—again, giving you every possible latitude of not being put in any position to guarantee dates and that kind of thing, as we try to look at the work of the committee in our next meeting, if you're talking 2000—early 2007, and we're now June-July of 2006—is there a point time where our input would be helpful to you? Is that input helpful to you in November, December? How can we—when is the time period for us?

MS. YOST: Well, maybe two places. One is that once it maybe reaches those final steps to help us get it over the edge and out to the public. And the other is really once the proposed rule is published, we would really value your input on approaches to inspecting the laboratories, any kind of educational materials that might be helpful to laboratories to meet the standards. Those kinds of things would be wonderful to have from you folks.

DR. TUCKSON: Lastly, and I'll see whether my colleagues have any other quick question, I would like—if it is possible—for two things to occur. First, could we circulate to this committee the summary work that our predecessor committee, the SACGT committee did, on this whole issue of CLIA oversight and these issues so that we will have that as sort of a background for how committees like our's sort of look at this?

MS. YOST: Mm-hum.

DR. TUCKSON: That's possible?

MS. YOST: Yes.

DR. TUCKSON: Secondly, Judy, could you give us a document—a succinct document that says here is what people like you view as the scope of what needs to be done in terms of assuring this appropriate oversight? What's in place today so you've got building block A, B, C, D, E. Then define the things that are not adequate and the things that have fallen through the cracks through no one's fault, FGHLM, whatever—I can't count—that was a mixed metaphor. So the things that are missing and then that will help, I think, all of us to sort of focus in on what it is that we sort of need to be commenting on. Is that possible we could get that?

MS. YOST: Well, actually if you look at the slides that you have there, there is a listing of the existing CLIA requirements.

DR. TUCKSON: Okay.

MS. YOST: I mean a very concise listing but in the earlier part of my presentation on one of the slides it talks about—it starts with personnel qualifications, I think.

DR. TUCKSON: Okay.

MS. YOST: It walks through what's already in existence. Not in great detail but at least to provide an overview.

DR. LEONARD: If you look at Joe Boone's slides--

DR. TUCKSON: Right.

DR. LEONARD: --it's in there.

DR. TUCKSON: Deborah is reminding us that in Joe Boone's it is there as well.

Emily, did you have a comment?

DR. WINN-DEEN: I just wanted to ask what the opportunity is for revving the regulations to take into account changes in technology, changes in the field? It has obviously been quite a number of years since the original recommendations were drafted and a lot of things have changed in the world of genetic testing and a lot of things are still the same but there's a lot of changes that have been happened. What's the process for continuing to keep them updated?

MS. YOST: That is a wonderful question because one of the difficulties we had was that it was a moving target as time progressed and it is a revolutionary field. Everything was changing so it was our belief that if we wrote probably broader requirements in the regulation that we could have more detailed information in what we call our guidance document because that's more easy to change. We clearly did not want to have something out on the street that was outdated before it ever made a final rule. So instead we were looking for broader guidance in the regulation and then by policy and interpretation provide the specific guidance to the laboratories and to the surveyors.

We develop our guidance document with a dual role. Our guidance document is number one for our own surveyors to use to assess quality in the laboratory but now we write the guidance documents—since 2004, we have been writing that document to also include information to help the lab meet the requirements and also to know what the surveyor is going to be looking at. So it serves a dual purpose and that's where I would see--and we can update that routinely. Whereby a regulation, as you know—I don't have to tell you—takes a long time to get out on the street.

DR. TUCKSON: Right.

MS. YOST: So that was—that's our thought process behind that.

DR. TUCKSON: Judy, I want to thank you very much. What we'll do is this: I'm going to take Debra's lead on this and what I'm going to ask is Sarah and the team, we're going to put together for you, based on Dr. Boone's slides, also Judy's slides, and the stuff that we did in the predecessor SACGT committee on this, a little sort of focusing document for the committee to sort of look at so that you—so that especially again—again I'm going to be like a broken record on this, especially for the newcomers so that you really get a sense of where this thing is.

I think what we'll do is we'll put that together so we'll have it in front of us and then the committee can decide based on our priority slide, which oversight is on that set of priorities, is where do we see the importance. And we will decide whether we really—how much—I think we're going to—we have to respond to Judy's request when she sends us stuff but we'll decide how much energy and how best to attend to this important issue as we go forward in the next meeting.

So with that, Sarah, we'll put together something and we'll get it out to the committee in the interim between the meetings and we'll take a good look at it.

Judy, we are looking forward to however we can be of help to you and thanks again for joining us.

MS. YOST: Thank you.

DR. TUCKSON: All right. Take care.

Let me note with very great pleasure that we have been joined by Dr. Janet Woodcock, Deputy Commissioner of Operations at the FDA. We're honored to have her with us this morning and we'll be hearing more from her a little later about the Critical Path Initiative as it relates to pharmacogenomics and so we'll be hearing some things there. In addition, she has kindly agreed to stay for some of our discussion. I know her schedule has got to be probably be very fluid but she is certainly—however long that she can be with us is terrific.

Janet, we sort of talked earlier before you arrived about the priority that this committee has to get stuff done and we are very, very appreciative of having senior leadership from around the—from HHS to be with us and to make sure that you help us to get things done. So welcome and thank you for joining us.

DR. WOODCOCK: Thank you.

DR. TUCKSON: Great. Let me reset the thermostat and look at the meeting agenda again so you can know what's coming and where we're trying—what we're trying to achieve for this meeting.

For most of today we return to our work on pharmacogenomics focusing again on the development of recommendations that we'll be making in our report to the Secretary on this topic. As part of this discuss there will be the comments that I mentioned from Dr. Woodcock.

This afternoon we'll be updated about our draft report on the policy issues associated with undertaking a large U.S. population cohort project on genes, environment and disease, which is currently undergoing public review and comment, and learn more about the environmental components of gene-environment studies from two national experts in this field.

Tomorrow we will pick up with our deliberations on gene patents and access, which we began in March. Debra Leonard and our task force on this topic have organized a session that will provide a framework for the decision that we need to make on this issue, namely whether we need to take further action on the concerns and questions we identified in 2004 about the clinical care impact of patents. So again just to focus you in, we have had a very long discussion, a very good discussion led by our subcommittee team on this issue of genes and patents, and now to focus in as you look at all the things that you could look at on that topic, we really see a need to look at the clinical issues associated with it and that's what we're going to have a very focused discussion on tomorrow.

Tomorrow afternoon we will hear about the progress that some key stakeholders have made in advancing the prospects for advancing of pending legislation to prohibit genetic discrimination in health insurance an employment. We'll also be updated by FTC, FDA and CDC about their working groups on direct to consumer as I mentioned in my opening comments.

Public comment sessions are, of course, scheduled for both days. Individuals who would like to provide testimony and have not already signed up should do so at the registration desk.

Now let me turn to Sarah to do the policewoman 101 function about the ethics rules, which she's very good at.

MS. CARR: I am going to be very brief. You all remember that before every meeting your financial interests are reviewed and we try to make sure that there are no topics that come up no the committee's agenda that might pose a conflict for you. So we always rely on you, though, at every meeting to be attentive to your interests and to make sure that something specific doesn't come up that might pose a bit of a problem. If it does, we ask you to recuse yourself.

Also, as you know, we're advisory to the Secretary of Health and Human Services. We don't advise the congress and as special government employees, which you are when you're here for meetings, you also may not lobby the congress. So just be careful not to do that while you're here.

DR. TUCKSON: We've got our eye on you, folks.

MS. CARR: And that's it. That's it. We thank you for being so careful about all these rules.

DR. TUCKSON: All right. Thank you.

With that, are we cool or do I need to tap dance?

DR. WINN-DEEN: We're just about there.

DR. TUCKSON: I think that means I'm supposed to tap dance for another second.

(Laughter.)

Let me just ask the committee, by the way, are there any questions that you have? Are you comfortable? Is the committee—do you understand what we're about to try to do? Are you okay with the direction? Are you feeling like you're locked and loaded on what we're trying to achieve? All right.

Well, with that, we are particularly pleased that Emily Winn-Deen continues to be our leader in the pharmacogenomics, and to give us an overview of update and efforts on our pharmacogenomics task force.

Thank you to all the members.

By the way, those of you that are again new, you will—if you have not already—have the chance—will be wonderfully participatory in a subcommittee and, oh, will you be so happy that you did.

**PHARMACOGENOMICS SESSION**

**OVERVIEW OF PHARMACOGENOMICS SESSION AND UPDATE ON EFFORTS OF THE SACGHS PHARMACOGENOMICS TASK FORCE**

DR. WINN-DEEN: Okay.

(Slide.)

Well, today I wanted to give an overview of what the pharmacogenomics task force has been up to and what we're trying to accomplish at the meeting today.

(Slide.)

So in the session today the first thing we're going to do is review the activities that we've done to date. That's going to be followed after my short introduction and review here. We're very, very pleased and privileged to have Janet Woodcock from FDA here to give us a briefing on the Critical Path Initiative and we also hope that she can stay for a little bit and participate in a Q&A session at the end of her talk.

After that, we're going to have about four hours during which we can discuss the draft background report that is in your briefing books, as well as the recommendations that we're considering making to the Secretary.

(Slide.)

So for the benefit of the folks who are just joining the committee, the task force really was formed in response to pharmacogenomics being identified as a high priority issue during our original vision setting activity. In June 2005, we had our first informational session and then that was followed by another session in the October meeting. In March 2006 we went through a very detailed review of what all the HHS agencies and other federal groups were doing with regard to pharmacogenomics since there is a lot of activity in this field and began a discussion of what things we could recommend going forward.

(Slide.)

So today you've gotten a report outline. Right now the Lewin Group, which was commissioned to write this backgrounder for us, has completed the draft report. What will be done with that is that it will be slightly reorganized and our recommendations will be interspersed into it at the appropriate places so there will be a discussion on the topic and then recommendations that go with that topic will be interspersed much the way we did with the coverage and reimbursement report. So that is the plan moving forward.

(Slide.)

The task force has looked through this report and given sort of the first set of feedback through a series of conference calls. We certainly would like feedback from the rest of the committee if there's anybody who has comments on the report. Either of things that aren't in there that should be in there or things that are incorrect that are in there. We definitely would like input from all the committee as well as

the ex officios so that we can continue to revise and refine this report.

(Slide.)

Since the March meeting the task force has been working with the staff to further refine the draft recommendations that we discussed in March. We've held several conference calls and we now have our intern who is working with us to help work on some additional recommendations. Those are the 13 new recommendations that will be discussed today. They are in your table folders, I believe.

(Slide.)

So just for reference, the literature review is at tab 4 of your briefing booklet and the original recommendations are also at tab 4 right in the beginning, and then the new draft recommendations are in your handouts that are at your place today. These include a number of straw man recommendations. Some of them are just sort of a topic and several options for what we might want to say on that topic. There's no meaning to the order in which those things are presented. They are just there as thoughts for what the committee might want to say from maybe a very mild response to a much more strong recommendation. So that will be the basis of some of our discussion later today.

(Slide.)

The next steps are really to try and pull this all together to use the literature review as a basis for what will become our pharmacogenomics report, to refine the recommendations so that they fit into that report, and of course to take all the input that we receive in the discussion during this meeting and use that as well to refine the draft recommendations.

The plan for the task force is to organize a day long session for just the task force in early September and then to really have finally put together a draft report and recommendations which we hope the full committee will give its blessing to at the November meeting and will then at that point be set out for public comment.

I should remind you that up till now the drafts that are in your book are drafts for internal discussion. They are not ready for going out to the public.

As part of our normal process, we'll have a public comment period and we'll take the additional feedback from the public comments and then try and finalize a report, hopefully, some time in 2007. I'm not sure exactly what the timing will be.

As Reed mentioned, I will be rotating off of the committee and Jim Evans will, fortunately, be taking over the helm of the task force. So he will be the person that you can direct all your comments, good and bad, to in the future.

DR. EVANS: Only the good.

(Laughter.)

DR. WINN-DEEN: Okay.

(Slide.)

Well, with that said, I'd like to now give Janet Woodcock a chance to come up and do her presentation on the Critical Path Initiative. This is a very important initiative that the FDA has undertaken to really try and move in the direction of understanding what the roadblocks are and trying to overcome some of those roadblocks.

**CRITICAL PATH INITIATIVE AND FDA'S VISION FOR PERSONALIZED MEDICINE**

DR. WOODCOCK: Good morning. Can everyone hear me? Okay. Good.

(Slide.)

I'm really happy to be able to be here and talk about our Critical Path Initiative because it really is in many ways closely linked to genetics and to pharmacogenomics, and these two things, although they're not exclusively the same, have a lot of connection.

I was asked to talk about the Critical Path Initiative with particular emphasis on personalized medicine and I think that's because the genetic part of this really does pertain to personalized medicine.

So first I'm going to walk you through some of the background quickly on how FDA got to have

this initiative and what the issues from our point of view are.

(Slide.)

Of course, I'm sure this committee has discussed in great length all the unmet medical needs that exist in our society and the fact that for biomedical discovery this is really a golden age and it isn't just the sequencing of the human genome but a huge variety of additional technological and scientific advances that have led to the generation of thousands, literally, of new targets within the body, new pathways. At the same time for medical devices for really unprecedented ways of investigating in the gene and intervening in the body mechanically or physically. So we have this tremendous burst of creativity and information at the discovery science level.

(Slide.)

In addition, recently published in JAMA the ten year investment in biomedical research has doubled over the prior decade in real dollars so our economy is continuing to pump investment into the biomedical R&D sector. Most of that in industrial, 57 percent, but quite a bit from the government, federal government, and some even state governments increasingly. And increasingly even from private sources such as Gates Foundation. So there has been a huge serge of investment at the same time that the biomedical science is really exploding.

(Slide.)

And this just shows a couple of trends of pharmaceutical R&D spending over the '93-2003, as well as the NIH budget. You can see the increases are somewhat parallel and this is reflected in other sectors, although it's not as easy to get the numbers.

(Slide.)

And everybody, the public and so forth, has been expecting a matching acceleration in products coming out the other end. I'm sure the insurers have been bracing themselves for this.

(Slide.)

This is what we see. This is the ten year trends in drug and biological submissions to the FDA. So this is not to say these are—the FDA is turning a lot of things down. This is what FDA gets in the door. Over the same decade I've arrayed the submission rate over the same decade I showed the investment. You can argue whether this is going down or is flat but we can all be in agreement this is not increasing. The submission rate is not increasing. This is biological products and drugs.

Devices look a little bit better in innovation but certainly not exploding. It's harder to array the device numbers in a reasonable way because they're so disparate.

(Slide.)

So this has been various called by people the pipeline problem or industry productivity problem or some kind of problem or whatever but, in fact, we're not seeing a matching acceleration in innovative new products coming to market that we would expect from this level of investment, which has been going on for several decades, in fact.

(Slide.)

And this is not a U.S. phenomenon. 2004 marked a 20 year low in introduction of new medical therapies--in other words, novel medical therapies into worldwide markets. Costs--at the same time that this slow down—we're observing a slow down around the world--and FDA, of course, has talked to the regulators, whom we know well, all over the world, Australia, et cetera, et cetera, and Japan, the Europeans, they're all saying this and are very concerned about it.

The costs to get a drug—a new molecular entity drug onto the market has exploded. Some people—these numbers are controversial but it really doesn't matter--the order of magnitude is correct, estimate that for every successful new molecular entity that has gotten on the market you have to invest about $1.1 billion and a lot of that is investing in the losers. It's about nine losers to every one successful product.

(Slide.)

Now for the purposes of society, even the broader society, worldwide society, the point is here this is disincentivizing investment in less common diseases, in smaller markets or in risky innovative approaches. Actually, I believe, except for the Gates Foundation and other charitable efforts we've seen recently, the interesting investment in, for example, treating tropical diseases has declined, oddly enough, over say a decade or so but when you look at the risk here, the financial risk that's borne by those who attempt to introduce these new products, you perhaps understand the structure.

(Slide.)

And in the face of all this new science, which is incredible new science, the product development success rate has actually declined so the risk is higher now.

New compounds—this is for drugs and biologics—entering Phase I development today have about an eight percent chance of reaching the market, less than one in ten. It had about a 14 percent chance 15 years ago. Now you might say those numbers aren't that different, and I agree they aren't that different but shouldn't we be doing better now than we used to be. No, we're doing—arguably we're doing worse.

Even more concerning is the Phase III failure rate. This is figures that industry tells the FDA. It's now about 50 percent versus about 20 percent a decade ago. In other words, half the products—the drug or biological products that are taken into the latest stages of development where there is the greatest sum cost, half of those will fail. They'll either be ineffective. They have an unexpected toxicity or their benefit will be so marginal they'll be deemed commercially nonviable.

(Slide.)

Now, again this—and contributes to the costs then of developing these new therapies.

When FDA looked into this—we feel that the problem here—we had long been blamed for a lot of this. Okay. So we had some maybe vested interest in looking into this. Biomedical discoveries are not being effectively translated from the bench to the bedside, and I think the numbers speak for themselves.

There's huge investment in biomedical research. There's a lack of corresponding new products available to patients. There are major increases I medical product development costs and a concomitant major rise in health care costs because, at least for the pharmaceutical and device sector, they have to obviously pass on their development costs into the products, their R&D costs.

(Slide.)

There has been a lot of speculation on what's going on. A lot of people think, and this is undoubtedly true, that genomics and other new scientific advances are not at their full potential. Unfortunately, our experience is it takes 10 to 15 years for some new scientific advances to really be applied, if they're just left to their own devices more or less, to benefit a development fully.

Some people say easy targets are taken, such as bacteria. There were naïve bacteria out there that were just waiting for penicillin. Chronic diseases are much harder to study and much harder to intervene on. That's obviously true.

There's also the issue that rapidly escalating costs and complexity decrease a willingness of sponsors and their ability to bring a lot of candidates forward so we're probably screening fewer than we were or not that many more candidates in people.

Mergers and other business arrangements have decreased the number of duplicative candidates that are developed because companies typically pick one when they have a portfolio of similar candidates to move forward.

Of course, some people still blame the FDA for this. It is absolutely true if there were no FDA requirements and you could put anything on the market you wanted that some people would do that without any testing whatsoever and the translation would be extremely efficient. However, there might be other societal tolls that would be taken by that approach.

(Slide.)

Our diagnosis at the FDA is that we've kind of outstripped ourselves that the investment and progress in basic biomedical science has really far surpassed investment and progress in medical product development, which is in itself a separate different process. The development process which we feels is the critical path between these discoveries and benefiting people in this country is becoming a serious bottleneck to delivery of new products.

Our explanation for this, to some extent, is that we are using the evaluation tools and the infrastructure of the last century and in some cases more remote than the last century to develop and evaluate this century's advances. So if we have new genetically discovered compounds and they go through a tremendous amount of sophisticated screening to look at their actions on receptor and so forth then we'll put them into animal toxicology to try and predict their safety in humans, animal toxicology being a science that has been around an extremely long time that hasn't changed very much in a very long time.

(Slide.)

So we feel that the science used to predict and evaluate product performance has not advanced at the same rate as basic science. In other words, that basic science hasn't been pulled in efficiently and applied to evaluating these products so this is causing developing to be the bottleneck.

We think, though, this is also an opportunity. There's an opportunity to improve product development with a new science but this is going to require a lot of paradigm shifts in the way we develop this applied science, something that we really haven't paid a lot of attention to in the past. "We" meaning the whole research enterprise, not the FDA.

(Slide.)

So we define a critical path as that series of steps that goes from candidate identification where you have a prototype device or you have a candidate drug or set of candidates all the way to where you get something on the market and there are a huge number of steps and it's extremely complicated procedures and efforts that have to be gone through to go from having that great idea. I cannot tell you how many times on this very campus I've talked to a laboratory and they've said, "I've discovered this and next year it's going to be available to patients." Of course most of these never become available to patients and there is a tremendous lack of understanding in the research community about what actually needs to be done to create a viable commercial product that actually can be marketed.

(Slide.)

It involves serial evaluation of the performance of the product through preclinical testing and clinical evaluation. If you look at it that way, whether it's a diagnostic device or whether it's a new type of imaging machine or a defibrillator or whether it's a drug or biologic or vaccine, you want to first predict how it's going to perform in people to make sure it's going to be safe enough to test in humans, and then you want to evaluate it in people and evaluate its performance to extrapolate, to be confident that you can extrapolate that to the wide number of people who will be exposed after marketing. That's really the task. It's a scientific task of evaluation and prediction and we don't have very sophisticated tools to do this. That's what I'm telling you.

(Slide.)

The Critical Path Initiative that we have developed focuses on the science that's used for these evaluations. It says how do we do these evaluations now? How can we do them better in the future?

(Slide.)

And, interestingly enough, a lot of the answers we've come up with have to do with genetics, genomics and personalized medicine, and I'm going to talk about that a little bit more, which I do have time, which is good.

(Slide.)

Here is a schematic of the Critical Path as we see it. Basic research is far on the left there and out of the research laboratories come prototypes, device prototypes or whatever, come discoveries of targets

and candidates that could potentially intervene on those targets to make drugs or vaccines or biologics. After those are refined a bit, you get into preclinical development. Starting right about then you're on the critical path. You've identified something and you want to start trying to figure out whether it is going to perform adequately enough to be a new intervention. You have to take that all the way through what people are familiar with, the Phase I, II and III of clinical development and so forth, or some iteration of that, along with you have to file a marketing application, and then you have to get the product approved usually if it's an FDA regulated product obviously.

(Slide.)

Now, what people really don't understand is that the science used to do this is different than either basic research science that's on the left or we've heard a lot in the past four years about translational research. And I was somewhat befuddled by this and I did a literature search on translational research and I've looked at what the NIH is doing and everything, and that's usually defined as research that moves a single product or set of products from the bench into early clinical development. So again translational research is often focused on what is needed to be done for a specific product or class of products to move them into the clinic and evaluate them in the clinic. That's very different than the tools that you would use to do that and that is what we're saying is a somewhat neglected aspect of science.

(Slide.)

We found that there are really three dimensions that you have to get your product to perform on and FDA is extremely familiar with all of these because this is our bread and butter. This is what we do all day.

First of all, you need to assess safety. You need to assess safety preclinically before you get into people and you have to have a pretty good prediction of that or you're going to get into trouble and you're going to expose human volunteers to excessive risk.

And then, of course, during clinical development you have to get a fair amount of certainty about safety performance of the product before it's set loose on the population.

The second one, proof of efficacy, is what people have spent historically most of their time thinking about and worrying about, and that's how do you show that the product works. Basically that it benefits people in the way it is intended to. And that's why you do randomized controlled trials and so forth.

And then the third issue has been completely neglected, in general, except in the industrial sector, we feel, and that is what we call industrialization. How can you manufacture a product at commercial scale with consistently high quality? And you may not believe this but this is not at all easy and if you think back to the flu vaccine problem a couple of years ago you can see that even highly motivated manufacturers can have problems with mass production of complex products.

FDA sees this over and over again. We have a constant stream of recalls and product quality problems that we are presiding over all the time. And shortages all generated by this industrialization problem.

This, for example, in genetics can lead to problems say with performance of diagnostic tests. If they are out of spec, they won't give you the right answers anymore potentially and we see this occasionally where we're recalling diagnostic tests, for example, because they have been manufactured improperly.

So these there challenges or dimensions on the Critical Path have to be serially addressed at greater and greater levels of performance all the way up to where the product is on the market where a very high level of performance needs to be sustained.

(Slide.)

Our initiative is a serious attempt to bring attention and focus for the need for all of us as a society to target some scientific efforts on modernizing the processes and methods that are used to evaluate these dimensions as the products move from selection all the way to mass manufacture.

I'm going to tell you a little bit about what FDA is doing in that and then I'm going to focus on personalized medicine.

(Slide.)

What we are doing is trying to stimulate, and we've been actually pretty successful in this, collaborative efforts among government, academia, industry and patient groups to get a lot of this work done. The work is focused not on product development, and that's what's very novel about this, this is focused on the infrastructure and the new scientific tool kit that we can all use to bring these products forward.

We're trying to build support for the academic science bases in the relevant disciplines. Some disciplines have really withered over the past 20 years with a focus on sort of reductionistic basic science and that has been fine. We have learned a tremendous amount from it. However, now we need animal physiologists. We need system biology. We need system understanding again and we lack some of those disciplines, clinical pharmacology and so forth. This one has been hard for us to do because these disciplines need financial support obviously.

One of the great tragedies that has been occurring, we think, is the lack of sharing of all the existing knowledge and databases that have been generated mostly in the private sector and not been shared. So we have a lot of information and data out there. We have very little knowledge that we've built on. If we have time, I can tell you about an animal genetic testing consortium that is going on for animal predictive safety tests and it's very interesting.

Finally, we need—then FDA needs to take this new science and turn it into new standards that then would be harmonized internationally and accepted in regulation around the world.

(Slide.)

What we've done is we published an initial report in '04. We had a long public discussion with both advisory committees, with the scientific community, with the industry and so forth. We started at that time initiating multiple public-private partnership consortia using nonprofit conveners to bring together these various sectors. As I said, we have been successful in this.

Recently we published the Critical Path Opportunities Report and List that can be found on FDA's website under Critical Path. I can get you a hard copy if you'd like. This is an analysis of the situation in fairly extensive detail plus a list which has 76 distinct opportunities, scientific projects, that we think should be completed that would really help move products to patients in a much more effective manner. Quite a few of those have to do with genetics in one form or another. So we're working to continue to form these consortia to do the—actually get the research done that's needed.

(Slide.)

Now we identified a number of opportunities for modernization of the process and here they are listed here. I'm only going to talk about biomarkers after this but these things are linked. Particularly the way we do clinical trials is going to have to change as we develop new biomarkers and bioinformatics is going to be needed extensively to support all this work in the future. I can tell you that neither of these structures—infrastructure elements are in place. We are working with the NIH, of course, on much of this and they've been very helpful.

But in biomarkers in vitro diagnostics is an extremely important aspect of this initiative and something we focus quite a bit about on to. Imaging is also a new and very important modality in the sense that we're going to move away from simply anatomic imaging, which is the kind of imaging that has been done mainly in the past, and we're going to be into functional imaging. We can look at different molecular probes of different types to look at physiology, pathophysiology and so forth using new kind of imaging technologies.

And then preclinical toxicogenomics, just to give an example of how using genomics—the C-PATH Institute, which is in Tucson, Arizona, that's headed up by Ray Woosley, and was founded to support critical path activities--it's a nonprofit—has formed a consortium as one of their projects. I think

the—I believe they have 10 or 12 major pharmaceutical companies in the consortium right now. What they are doing is they have developed a mechanism with all the appropriate intellectual property and antitrust arrangements for these companies to pull their assays and data on animal toxicogenomic tests and related tests that have been developed to better predict toxicity in the animal testing.

What they will do—they're going to round robin cross validation testing using each other's assays in their own systems to look at their predictive value and then they're going to select the highest performing test, and those will be submitted to the FDA to hopefully begin the start of a new battery of tests to look at major organ toxicity in animals to better predict human safety.

Some of these tests, depending on how accessible they are from kind of the periphery of the organism, may then be used for human testing as well to monitor and predict human organ toxicity. So that is a very nice consortium and the point is—the real point of it is all these tests and data which are very cutting edge and using the most modern science were sequestered away in different pharmaceutical companies had not been shared, the data were not available, this consortium will make all its data and the assays publicly available at the end of their testing period.

So we're trying to set up consortia in all of these areas and we're slowly—the FDA does not have any funding to do this initiative, although there is some money in the President's 07 budget and we are hopeful perhaps we will receive some funding to do this initiative in '07.

(Slide.)

Now I want to talk about biomarker qualification because this is the heart really in my mind of personalized medicine. Biomarkers can be defined as quantitative measures, a physiology, pathophysiology, all sorts of stuff. Quantitative measures of something about the person and their biology. An example that we have now are things like liver function tests, ECGs, x-rays, psychological tests. These are quantitative biomarkers that we use to assay some state of the individual.

The problem we've observed in the past 20 years is that biomarker discovery is fast. If you read the medical literature and scientific literature, you'd believe there are thousands of desirable and wonderfully predictive biomarkers out there, and we can tell everything about people based on all these biomarkers that have been discovered and their wonderful associations. Unfortunately, clinical meaning develops very slowly as an understatement. Not at all—okay—might be a better description of what happens with biomarkers. We get all this very tasty, suggestive publications that are written up in the newspapers and the public thinks, "Oh. We're going to be able to tell whether I'm going to have an MI in the next week or so or whether I'm going to get ovarian cancer," or all this kind of stuff, and yet 10 years later nothing. We haven't advanced any further.

And then, of course, you can always blame the FDA for this. The FDA hasn't approved them but we're finally pushing back and saying, "We don't approve things that don't have data associated with them."

The problem—the reason that clinical meaning develops very slowly is to really understand the clinical performance of a biomarker means you have to study it and it is expensive and it is grueling and it is not considered novel say by funders. It's not something that you win Nobel Prizes for doing.

But new biomarkers are key to personalized medicine because, I think, as Americans, we tend to forget—although I'm sure this committee doesn't forget—but that diagnosis is the foundation of medicine, not treatment. Okay. And you really have to know what you've got before you intervene and we have been rushing to develop treatments and we have not been rushing to figure out all the things we need to know about people before we intervene and treat them.

But there are very few parties that have the wherewithal to develop new biomarkers clinically and, therefore, that's why we think consortia are needed to develop them because there are many parties that will benefit from their development, not to mention the patients.

(Slide.)

So by "successful biomarker qualification" we mean understanding the biomarker's utility or

fitness for any given use. One of the problems with biomarkers that everyone is obsessed with is surrogate endpoints, which are biomarkers that could be used for drug approval in lieu of effectiveness. That's almost irrelevant to what we're talking about here. What we're talking about here is understanding pathogenesis, for example. We're talking about understanding biology using these diagnostic probes.

New biomarkers obviously are critical to clinical medicine, I believe, to its efficiency and effectiveness, and efficient product development. So this is a place where I believe that kind of the stars are lined up that the manufacturers of therapeutics have the same stake in the development of new biomarkers that the insurers, patients and the public do, which is we all need them and they will tremendously improve medicine if they can be developed.

But as I said there is no single entity charged with accomplishing qualification. As you all are probably acutely aware, the diagnostic companies regard their task primarily as analytic validation while making sure that the test performs and analyzes the analite correctly. That's a very important step but it doesn't tell you what the analite means but we all have a big stake in making sure this gets accomplished and this is a big part of critical path.

(Slide.)

What am I talking about? I can get extremely concrete but I was only given a half hour or something like that so I will—how long do I have by the way? Until 10:30 or am I over my time already?

DR. : No, you're fine.

DR. WOODCOCK: Okay. Good. Okay.

What I mean is, for example, in pharmacogenomics—the very simple one is the pharmacogenetics, okay, that have to do with just the gene sequence and variability and the gene sequence could even itself, leaving aside genomics, be an extremely powerful tool for development and also for improving the quality of health care.

Many of us have differences in how we dispose of drugs after we take them. I imagine some people in this room are laypeople. Okay. So actually lots of doctors don't know this so this will be very comforting to you but if we all in this room took a drug, all right, some of us if we took an average dose would get the average blood level, the average exposure, okay. Others of us might get five times that level. Okay. Why? Because our disposal mechanism is different due to genetics. We dispose of the drug much differently, much slower. And those people are the people who get a lot of side effects obviously from some of these drugs. Other people who are rapid metabolizers—in other words, their disposal mechanisms are hyper efficient—they get no detectable blood level at all from taking an average dose. So they might as well not bother. Okay. They are just chewing up the insurance company's money. But it's really those people who have variable levels of metabolism. It's not average that are exposed to higher risk.

The Center for Devices at FDA has approved some of the—Steve Gutman and company have approved some of the first drug metabolism polymorphism tests. They are available. They can be applied to, for example, very important drugs such as cancer drugs where there's a lot at stake. You really don't want to have four to five times the blood level for a drug that has a neurotherapeutic index.

FDA right now is looking at trying to do a clinical study on blood thinners, warfarin. Warfarin is one of those compounds that is obviously associated with a lot of side effects. It requires a lot of testing and fussing over by the health care system to keep people from getting into trouble and yet maybe about 40 to 50 percent of the variability in the response to warfarin is genetically based and now there are tests available. They are not quite commercially available and they're not FDA approved tests, in general, but there are tests that can sort this out. But people have told us, and rightly so, they would like some documented proof of this and so a number of parties are pursuing doing some clinical trials to look at how much we can improve warfarin outcomes using pharmacogenetic directed dosing.

So that's drug metabolism polymorphisms and there are many others so there's a big opportunity here. A lot of these are for approved drugs.

For example, a long time ago FDA—when we approved the tricyclic antidepressants, the recommended dose was 25 to 250 milligrams. You say, "How can that be? What kind of recommended dose is that?" Well, that was because those drugs were subject to polymorphic metabolism and so you had to titrate everybody around probably for a long time. These may be people who were severely depressed, though. This was a very bad situation in the sense that many of them needed urgent intervention.

So that field is coming along. FDA—between the Center for Drugs and Center for Devices, we have done like a huge amount of things, which you may know about and your subcommittee may have talked about, to try and push this along because of the implications for safety of the populous and better development of products.

The second large group of tests would be predictors of drug—genetic predictors of drug response or nonresponse. In other words, this is targeting therapy towards those who would respond or away from those who don't stand to respond to a given treatment.

Again, the industry, the pharmaceutical industry, was not very enthusiastic about this for a long time because this would narrow the population, maybe about 50 percent, maybe in some cases 90 percent of the people who would currently get the drug won't get it at all. Okay. But from a societal point of view that's good. Okay. We don't want to give drugs to people who don't respond and I have—I ran the Center for Drugs for 11 years and I can tell you that the treatment effect of many drugs is very small but that's probably not because they don't work. In most cases it's because there are a lot of people in there who may not respond to the drug. So if we could find a way to weed those people out and not expose them that's targeted therapy and that, again, is personalized medicine.

Cancer is probably on the cutting edge of this. The problem with cancer is you're looking at the tumor. It's hard to get pieces of the tumor all the time to keep testing it to see whether it's going to respond to various therapies or not but cancer—we are working in cancer in consortia to try and get some targeted tests for targeting therapy developed.

And then a third category is genetic basis of adverse events. We're working with NIH and with the pharmaceutical industry on this, especially some of these rare very serious adverse events. We've always said they were idiosyncratic and that's a doctor's term for meaning we're stupid. We're too stupid to know what causes them so we call it idiosyncratic. But, of course, everything from a scientific standpoint has a cause and some we believe are these very serious rare adverse events that cause drugs to be pulled off the market. Probably everybody doesn't get a side effect. The vast majority of people don't get the side effect, just some people. And so there's some reason and we think in a number of cases there's a genetic basis that we can sort out.

(Slide.)

Advanced imaging is another thing that we're going to see more and more frequently. We may get imaging that can distinguish, frankly, certain genetic abnormalities at some point in time but we're not quite there yet.

(Slide.)

Now how much more time do I have? Be honest with me. Should I just wind up right now?

DR. WINN-DEEN: It depends on how long you can say after you finish.

DR. WOODCOCK: Okay. I can stay. I can stay as long as you like. All right.

DR. WINN-DEEN: So we're scheduled to take a break at 10 something, 10:35, which is almost where we are now so what I'd like to do is let Janet finish and have a short Q&A and then we'll take a break maybe a little bit later. That just moves our discussion off a little bit for the late morning.

DR. WOODCOCK: I'm sorry. I don't mean to go over.

DR. WINN-DEEN: No problem. No, we're delighted to have you.

DR. WOODCOCK: There's so much one can say about this. I feel that people need to understand if you're talking—I'm shifting a little bit to personalized medicine giving this whole thing as

background that I just showed you, the role of genetics in the Critical Path Initiative.

We have to recognize that the way we look at drugs and devices and biologics and everything in development—the development is the parent of the clinical use or the clinical use is a child of the development process, however you want to look at it. So the way we approach things now leads to much of the way they're used in health care.

What we do now is the randomized controlled clinical trials to determine efficacy and to a great extent safety. And these were really scientific—what we used to do, which embarrassingly enough, up to '60s, we basically used sort of anecdotal reports to—I don't mean "we" FDA. I mean "we" the society used anecdotal doctor's reports to determine how well things worked. So this is really what has lifted medicine up into its current state of science but don't forget this is a population-based model that's used to control for not only bias but the impact of variability. Much of the—a lot of this variability actually is something that we'd like to know about nowadays. This is at the heart of personalized medicine so instead of controlling for variability simply by randomizing and then making all the recommendations just for the population that you enrolled, you really would like to understand the variability. Part of the problem, though, is we've gotten so enamored of the randomized clinical trial and how we do that on this population basis that I believe we've stopped thinking about the fact that many of these variations are actually extremely informative.

(Slide.)

Now there are limitations to controlled trials and that's what we're up against as a society. You can answer theoretically any question with a controlled trial. You could decide whether to get up in the morning, probably by using a controlled trial, but it's not an efficient way to do business. You can only answer one or a few questions per trial. Unfortunately, there's an unlimited number of questions about the appropriate use of medical products and about the outcomes of use of medical products and these questions change over time. They are not static but there is a decidedly limited universe of funding patients, investigators, time and resources to conduct randomized, controlled, empirical trials to answer all these questions. If you read the medical literature, they always use a ritual phrase at the end of every article, which is more research is needed on this question to answer it definitively.

(Slide.)

Now this is true then for medical product development, drug development and other development. Okay. We're making compromises when these things are put on the market because it is impossible to answer all the questions. In fact, at the end of most drug development programs and biologicals, after these huge expenditures of resources that I've told you and also huge expenditures of time, it might be seven years or so, we don't know very much about the product. Everybody has been criticized a great deal about this recently in the drug safety uproar and so forth but this is the facts because we've done a lot of randomized trials and we've done a lot of empirical study and we do not have a lot of mechanistic knowledge.

We're usually quite confident that the drug or biological has a measurable beneficial effect in a described population of people who are treated in the trials but the overall treatment effect is often very small and we don't know, for example, often whether a few people responded a lot or whether a lot of people responded a very tiny amount, and that's extremely important as to whether you actually want to use that drug on people in the future but that isn't really how it's set up now. You can have a very tiny response and a lot of people and get a statistically significant result.

But as a result of all this, which I still want to emphasize is the best we've ever had and is a scientific triumph, nevertheless, often many people who take drugs after marketing don't benefit—aren't going to benefit from them.

(Slide.)

So we—I'm going to skip over this. I don't have enough time.

(Slide.)

So this leads—this whole empirical approach to medical product development leads to a lot of things. It leads to part of the health care cost controversy because we can't quantify the actual value of products in the marketplace. I think that we're—and this is something, I think, this committee needs to evaluate that the health care policy community, in general, has a very pessimistic attitude about technology and believes it leads to greater expense, lower productivity in health care and maybe not better outcomes for patients.

So the implications for genetic testing, for example, I think, are very important and whether people are actually willing to pay for that.

This also exacerbates a lot of the safety controversies that are out there because products are viewed as safe or unsafe for the entire population. There's no appreciation of the effect of human variability and its affect on safety. The reason is because we don't know those relationships.

Finally, I think, in health care quality this—I'm a physician and I learned a tremendous amount as I did drug regulation and I really think that all the confusing results and conflicting reports we have out there based on all the empirical tests that we do and so forth lead to an anecdotal approach to care. You can think of the estrogens, for example. I think physicians just think I get so many conflicting reports that I just can't sort my way through this and I'm just going to do whatever my anecdotal experience tells me is the best thing to do.

(Slide.)

What we need to do in development to help this situation is have more—pair more diagnostics with therapeutics as they're coming through the pipeline and a lot of this means more genetic and beyond genetic, probably proteomic and so forth evaluation. We need to identify—both identify the response of subgroups and prevent toxicity.

In other words, to put this a different way, we need a more mechanistic model of how products work. We need to put all our effort really into developing as much mechanistic understanding as possible. To do this we're going to have to change the way we do trials to have adaptive designs so we can answer lots of questions in the trials rather than just answer one question. Those questions are going to relate to who should be treated, who shouldn't be treated and so forth in a serial manner.

(Slide.)

For the development process then, this can improve the success rate, which is like the most terrible problem the development process has for drugs right now, and lower development costs but at the same time having products come out of the pipeline with more information rather than minimal information but we need to continuously improve development science and processes or this slope I showed you at the beginning of this talk is going to continue downward.

(Slide.)

But for patients this will result in more personalized treatment. What we need to see is much larger treatment effects using targeted therapy. In other words, if you have cancer or whatever and you are going to have your tumor treated with a certain regimen, you need a very—we need to move to where there's very high probability of a positive response.

We also, with many of these biomarkers, will be able to stop therapy that is ineffective faster. Right now, again, treatment is empirical. We just take the population. We expose them for quite a long time and maybe they respond and maybe they don't, and then we switch them. Using biomarkers we'll be able to interrupt that cycle much faster.

Avoidance of side effects and injury from these products through prevention and better and earlier product availability, and overall I think this will lead to higher quality health care as we have more mechanistic understanding of our treatments rather than empirically treating people.

So I think we hear a lot about improving health care and health outcomes in this country through all the things people talk about all the time over on the right hand here but I think the left hand, the development process, which is completely ignored almost in most health care policy discussions, is

another pathway to improve health outcomes by doing a more scientific job on the development side so that's what I have to say.

Thank you very much.

(Applause.)

**Q&A**

DR. WINN-DEEN: Thank you, Janet. Could you take maybe five minutes of questions before we take a break?

DR. WOODCOCK: Yes.

DR. WINN-DEEN: I just want to see if anyone on the committee—Debra, then Julio.

DR. LEONARD: Very interesting. What is going to happen to the opportunities list? I mean, correct me if I'm wrong but I don't think of the FDA has a funding agency.

DR. WOODCOCK: Right.

DR. LEONARD: So is this linked at all to NIH funding? Is it linked to other sources of funding for these types of opportunities because it's a very exciting and interesting list?

DR. WOODCOCK: Right.

DR. LEONARD: But no one is going to do it just because FDA says, "Oh, wouldn't that be cool?"

DR. WOODCOCK: Right. Well, what we think was that—see this was a problem that nobody knew about in some way and what we needed to do is reduce—we discussed this problem in our first Critical Path report. We wanted to reduce it to some level of concreteness so people would understand what needed to be done. And, no, FDA is not intending to do almost any of this work. Sometimes we do laboratory research for product characterization issues in the manufacturing so we develop the standards for product performance in the manufacturing realm but the clinical work, the toxicology work, we're not going to be able to do that but people are stepping forward. I mean it's slow but we're seeing a ground swell of people working on this in consortial arrangements. We are working very well with NIH and we think that as people begin to understand this problem and the criticality of this to health that this will build over time but we don't expect this to happen overnight.

DR. COLLINS: So I very much agree that this is an area of intense need and I think what FDA has done here by outlining the agenda is an extremely helpful step forward. It is sort of an odd circumstance where having outlined the agenda, the FDA is not in a position themselves financially to push the ball forward and, therefore, are dependent upon building these consortia and working with other agencies. Obviously that in some instances slows down the process because you have to cajole instead of offering the bucks that might otherwise stimulate the process and perhaps that a bit of an unusual circumstance.

I think the need is so great that you do see various organizations rallying to make this happen and certainly NIH has been enthusiastic about many of these priorities and has been working closely with FDA to try to make them come forward. The mention of the warfarin trial, for instance, is something that we're trying to do together which I think will be actually a very interesting poster child for prospective pharmacogenomics.

I guess, Janet, could you say a little bit more about the Critical Path Institute as another player here in terms of an organization not for profit that by its very name is designed to try to fill some of this void and how are they funded and what kind of opportunities do they have and where do you see the challenges for that organization in terms of just stepping into the void here and making all this happen?

DR. WINN-DEEN: Well, the C-Path Institute is a 501C3 nonprofit. It's funded for its staff and so forth by the City of Tucson, the State of Arizona. It's funded by nonpharmaceutical, nonindustry sources, and charitable funding as well. For projects it's putting together a consortia that would be funded by the various partners for the projects themselves and the toxicogenomics is obviously the one that is farthest along but they are doing—they got a small earmark in FDA's budget this year from

congress to do genetic cardiac safety biomarker work using the University of Utah's large genetic database that they have. So that work is ongoing. As well, they're participating in the warfarin project and they're also starting to work on targeted therapy and putting together a consortium on that, which is very exciting. But we do not see any one source being the central group doing this. We see a wide range of groups around the country working on different projects depending on the level of interest.

DR. WINN-DEEN: I think Julio had a question.

DR. LICINIO: Yes. I had a question about the issue of safety that you presented in one of the last slides because it's such a—nothing is completely safe.

DR. WINN-DEEN: Right.

DR. LICINIO: And where do you draw the line? Especially with pharmacogenetics it can become complicated because what's safe for one group may not be for the other and then you get into the accuracy of the test and are the people going to take the drug irrespective of the testing results.

DR. WINN-DEEN: Right.

DR. LICINIO: So can you make some comments about this issue and how—I think now especially—I don't know if you have the same impression that people have this expectation of increasing safety but nothing is completely safe and it's never going to be. So how do you—where do you draw the line? Where do you draw the expectation then and the line from the regulatory perspective?

DR. WINN-DEEN: Right. Well, of course, no medical product is ever going to be completely safe and has a benefit/risk analysis associated with it. I think we can improve the benefit/risk remarkably. If you have an expectation of significant benefit, even if the risk remains constant, your judgment of the overall benefit/risk for you is improved.

I think, though, that pharmacogenetics and genomics and related sciences will improve the safety and I recognize I've heard these concerns many times. We don't know the link between that and clinical outcomes. People won't have the tests. Other people will take the drug regardless. That's all true. But I'll tell you it's better than guessing and that's what we do now. We have no idea why people get adverse events and what are the risk factors in a given population. Except for you could say age, debility, multiple medications or so forth. We don't have the mechanistic links between bad outcome and some kind of genetic or other predisposition.

The more mechanistic understanding we have both on the efficacy side as well as the safety side the better off we're all going to be. I really strongly believe that.

DR. WINN-DEEN: Reed, did you have a question?

DR. TUCKSON: First of all, again, thank you very much. I mean your first slides are actually mind blowing. I mean, I don't think that—at least I don't think many people—I certainly know that I did not understand that with all of the research that's going on, all of the stuff that's coming down the pipeline into clinical medicine today that is expensive and complex that the actual fall off in the amount of stuff coming to you all is that dramatic. I mean, it's astounding information for those outside of your world.

Now having said that then I think your—if I understand the big 8,000 foot level of your point that—maybe it's two, and one is that part of the problem is that there needs to be a more precise ability for developmentors, manufacturers to predict earlier on whether or not their product has actually got a dooby-squatch chance in heck of working so they can target their efforts more effectively, which is a big important industry deal.

And then, secondly, they have to be better tools for you to evaluate them to be able to do that more quickly, more efficiently and more effectively.

So if those are the two big take homes here then I think the committee needs to sort of be thinking about what we—if there's a role for us here and what that might be to be able to go forward. First of all, this has been enormously good just as we understand and learn this and begin to think about what pharmacogenomics means going forward so I think that our challenge is, as you are in the break and as

we start to have discussion coming back from the break, is what can we do with this.

I think Francis' question about is this the time for—he has given us some sense that there's some cross HHS coordination now. I suspect that, like most things, we might be able to urge a finer point on that, I mean, but it sounds like that's encouraging. Either we need to support that to the Secretary or urge some new things to be done or some more energy be on that.

I think secondly coming out of what you sort of said, Janet, is the sense of some industry—some multi-stakeholder conversation about this, which sounds like it's in everybody's interest, not only the folks who are in the industry but those outside of the industry and perhaps that is something that we might want to kick around after the break.

DR. WINN-DEEN: I would add there's a third high level point, I think, which is, number one, there's a huge problem—the pipeline problem. Number two, we need these better tools at the manufacturers and we need the evaluative tools.

Number three, I think it's really important that this has the potential to transform the way clinical practice is done if we can gain more understanding of what we're doing with therapeutics.

DR. TUCKSON: By the way, Janet, I sort of wanted to give you the chance. I don't know whether you can in public any more but the sort of sense of the degree to which you feel that the collaboration with—I sort of made that rhetorical as opposed to whatever a question is—but is there anything else that you might want to say in terms of opportunities that you see either now or later for more coordinated activity across the enterprise, including the Agency for Health Care Research and Quality?

DR. WOODCOCK: Yes. We're having terrific collaborations. I think an unprecedented level of collaborations I would say with NIH and the various institutes around these issues because at the same time that—I mean we have the Roadmap Initiative pushing on one side on the translational centers and on other things but here we have the basic sciences really starting to intersect with the therapeutic science, the clinical science, in a way that we haven't seen before. We can actually start making those links in a much more direct manner and, therefore, I think there's a real opportunity to collaborate.

I think a lot of this is limited right now by FDA's extremely limited resources.

DR. WINN-DEEN: We'll take one more question before the break. Steven?

DR. TEUTSCH: That's great, Janet, and appreciate all your thoughts about this. I'd like to ask you if you couldn't comment a little bit, though, about what we continually call the fourth hurdle in drug development, which is getting it out and demonstrating its value particularly to payers.

DR. WOODCOCK: Right.

DR. TEUTSCH: And payers, of course, are becoming ever more sophisticated, which is great from the societal perspective and they want to see outcomes and they want to see incremental outcomes.

DR. WOODCOCK: Right.

DR. TEUTSCH: And some of the things that you're talking about obviously can do that for subpopulations and becoming more specific but as we know currently only about 30 percent of the things that actually do get into the marketplace are commercially successful today.

DR. WOODCOCK: Right.

DR. TEUTSCH: And this is going to become that much more challenging if we, of course, get them for ever smaller populations. So the genetics and the kinds of things you're talking about will be—will hopefully get some efficiencies on one level but it's still going to be a real challenge to get those kind of outcomes, particularly with the challenges in biomarkers like you said. The biomarkers, of course, are only one intermediate. I mean as you were mentioning coumadin, you can look at the genetics but we all know there are so many factors that lead to differences in coumadin level. You sort of ask yourself why don't you just measure the coumadin levels rather than having to—looking at just again one piece.

I think the challenges of all this are great and clearly the kinds of things you're talking about are a major step in one part of it but it raises—the industry is under a lot of challenges of this sort to figure out

how to make this all work in a commercially successful manner.

DR. WOODCOCK: Right. I agree. I have listened to several health economists present analyses of the economics of this new way of doing things and with some very modest assumptions on the pre-market side that is an increase probability of success. I already presented to you all at least for drugs and biologics how low the success rate is now. You can improve your probability of success modestly if you are targeting. The economics are favorable. I think this is why a number of large companies have started pursuing targeted therapy.

Also, the economics would be favorable if you can improve the treatment effect significantly because then you have demonstration of the value of the treatment a priori.

But the devil is going to be in the details on all of these and having talked to the insurers I think we're going to have to demonstrate a lot of this in clinical outcome studies that show the benefits, not just—I'm obviously—because having run the Drug Center, we approve all generics based on blood levels. So I believe that if you can—the blood levels are an adequate and well validated surrogate for effectiveness and safety but everybody else apparently doesn't believe that even though they push generics all the time. I mean if you can show that through pharmacogenetics you can tighten the blood levels very significantly. That's good enough for me but it obviously is not good enough for the outside world.

So we're going to have to do some outcome studies and some other things. Like everything else, this is going to take longer and be a rockier road than we all might hope but the promise for patients is so significant that we have—I think we have no other choice but to like push this as hard as we can.

DR. WINN-DEEN: I think that's a perfect place to stop.

We're going to take a ten minute break and come back about five after 11:00 and we're going to start with the recommendations that pertain to FDA while we have Dr. Woodcock here to help with that discussion.

(Whereupon, at 10:58 a.m., a break was taken.)

**FULL COMMITTEE DISCUSSION**

DR. TUCKSON: We are reconvened so those of you all that are feeding your faces in the back room, it's too late. We're starting.

DR. WINN-DEEN: Okay. So what we wanted to do now was to go through some of the recommendations and we've got—I'm moving along past where I am in my slides here, the goals of today's discussion. Okay.

So we want to review the remaining issues and gaps. I think Janet's presentation really filled in some of those gaps very nicely for us. I appreciate that.

What we'd like to do is go through and consider the recommendations that we had made which basically touch on things that we might be asking FDA to look at so that while we have a couple of people here from FDA we can get some responses, and then we'll continue after lunch with the rest of the discussion.

(Slide.)

So the goal is to discuss—what we've done is we've integrated our old recommendations which are the ones we discussed last time with the new straw man recommendations. The old recommendations have numbers. The new recommendations have letters so that's how you'd be able to distinguish. I do know the difference between numbers and letters.

(Laughter.)

Our goal really is to discuss the recommendations and understand your comments and your feedback, not to make this a wordsmithing exercise. The task force and staff will take all of the comments and critiques and everything that you give us as feedback and try and really work on the wordsmithing in our one day meeting in September.

And then the other important thing is if anyone on the committee—particularly since we have

three new individuals joining us this time who maybe have some new thoughts to share and new perspectives, if there's anyone who has some additional things that they believe we should be addressing, we're going to open that up for discussion as well.

So before going on to discuss the recommendations, Gurvaneet, who has been part of the task force, wanted to say a few words and it actually dovetails very nicely with what Janet discussed earlier today about whether we should be integrating more commentary and discussion of the impact of this on the drug development process and not just on the other end of the practice.

DR. RANDHAWA: Thank you, Emily.

I'll try to be brief in my comments here. I'll offer two sets of comments, one from an AHRQ perspective and one more from my own perspective.

So as everyone around here is aware, AHRQ's mission is to improve the effectiveness, safety, quality and efficiency of health care. One of the ways AHRQ does this is by clarifying the evidence of health outcomes of the different clinical interventions to inform decision makers and policy makers to make evidence-based decisions.

One of the points that I totally support what Janet had said was there is a need for evidence on health outcomes and not just surrogate outcomes. You will pretty soon see an example of a study that will be circulated to you which, to me, illustrates the difference between these two for pharmacogenetics. So the study is an RCT which was done on pharmacogenetics of codeine metabolism in children who underwent tonsillectomy. The researchers looked at not only the plasma concentrations of morphine and metabolites but also the pain score of the children and their need for relief analgesia. What the study showed is that there is a significant association of the predicted phenotype based on the genetic testing and morphine blood levels. There was no significant association of the predicted phenotype or the blood levels with either the pain score or the need for rescue analgesia. So this just illustrates, I think, some of the challenges that we have in translating surrogate outcomes to health outcomes.

I believe the underlying issue for the recommendations—the old five, six and seven recommendations was to try and understand how we gather and synthesize data on health outcomes of clinical interventions, be they drugs, diagnostics or biologics after they have gained regulatory approval. So sort of post-FDA approval.

Now typically the Phase III trials focus on surrogate outcomes in highly specialized patients and they do not analyze long term outcomes or real outcomes in the general population. So we need data once FDA does their approval of the medical products, we need data in the real world and this data can come in many different study mechanisms. It can be through the practical or pragmatic clinical trials. It can be through registries, administrative databases, health plan databases, electronic health records, and even supplementing existing RCD data.

So each one of these study designs has its limitations and advantages. I think the recommendations from the SACGHS need to address them.

A related issue is the nature of public-private partnerships that we've been talking about. How do we all work together to gather data on health outcomes? One of the recommendations mentions the Coverage Evidence Development Initiative from CMS, which in my mind equate that with conditional coverage when the payer, whether it is CMS or it could be a nonfederal payer, covers a clinical intervention contingent upon the patients being enrolled in a study to evaluate outcomes. So that to me is conditional approval.

The implication here being that if the clinical outcomes are shown to improve then there will be a broader coverage decision made and the reverse would be true if there was no effect on clinical outcomes.

What I would like to propose for the SACGHS is to explore these issues further. One is the conditional coverage. Can we think about doing this outside of the CMS setting in a broader setting? A related issue is conditional approval.

Now before I venture further, let me make it clear that I'm discussing things that are not within

AHRQ's purview. We do not make coverage decisions nor do we have any regulatory powers to make any decisions to approve medical products.

So to me clinical coverage is just one form of public-private partnership used to conduct studies to understand the impact of a new technology on health outcomes. So this would be classified as Phase IV studies. However, is it feasible for us to think that there may be a role of similar public-private partnerships in conducting studies earlier than the drug development pathway in Phase III or even Phase II studies?

So in my mind if you are to consider those kind of studies then we need some sort of a permissive environment of a conditional approval. Perhaps that is not feasible or possible but I think it's worth for the SACGHS to discuss it.

I would also like SACGHS to consider broadly beyond what I've described in terms of potential public-private partnerships in all the process from basic research to health outcomes. For example, one of the pressing needs in the biomedical research right now is the lack of standardized tissue and sample repositories. So if we are to have these repositories available to biomedical researchers, be they in academia or in industry, then that will greatly facilitate our understanding of the molecular pathogenesis of disease and also identify critical targets for drug development and perhaps even have validated diagnostic tests as they are being developed. I would urge SACGHS to consider making a recommendation on this.

Finally, I would like to ask the SACGHS to prioritize the potential public-private partnerships as well as its own pharmacogenomics recommendation based on their potential impact, anticipated time line to achieve that impact, and current resources available to implement these recommendations.

So, for example, should there be an equal focus on using pharmacogenomics to identify targets of drugs and also for dosing of drugs, to some extent this is a discussion on the relative contribution of pharmacokinetics and pharmacodynamics, and of germ line and somatic genetic variation in health outcomes.

When we are discussing rare genotypes and how they can potentially affect drug dosing, is that something to be done for all drugs that are developed or should we prioritize some of these drugs based on criteria such as narrow therapeutic index or potential for causing severe harm, et cetera?

And perhaps more importantly should this analysis array genotypes be done prior to FDA approval or after FDA approval and in what context?

So thank you for considering my comments.

DR. WINN-DEEN: Okay. Thank you, Gurvaneet.

(Slide.)

What I'd like to do now is to move through the first issue that we wanted to discuss which is the issue of co-developing diagnostics with pharmaceuticals. I think this is something that the comments that we've heard so far this morning leads nicely into is really when do you want to introduce biomarkers to that drug development pipeline? When do you need a validated test? When do you know that test is going to be worthwhile and provide you with some useful information in terms of patient care?

DR. TUCKSON: Emily, can I just ask you one just sort of focusing question here just so we're all on the same page? So I think we have two different documents of recommendations and I want to make sure we're all following. Some people are looking at the yellow pages in their tab 4 booklet. I have a feeling that's old.

DR. WINN-DEEN: Right. So we have—yes, you are right. There is two different. There is the first two pages in your yellow section of tab 4, which are the old recommendations, and then in your table folder there is a handout of the proposed new recommendation.

MS. GOODWIN: They are all in the table folders.

DR. WINN-DEEN: Oh, are they all together? Okay.

DR. TUCKSON: So the bottom line is what document should we have in our hands, Suzanne, so

we know where we're tracking?

MS. GOODWIN: You should have the white copy in your table folders.

DR. TUCKSON: Called?

MS. GOODWIN: Called "Possible Topics in the Straw Man Proposals for Additional Recommendations."

DR. TUCKSON: All right. Great.

MS. GOODWIN: The first four—sorry, the first five pages are the "new recommendations" and on page six to page eight are the old recommendations.

DR. TUCKSON: Okay. So again you've got a document that has the old recommendations are in the back of this document, the last couple of—two pages. The new version of it is in the front of it.

MS. GOODWIN: Right.

DR. TUCKSON: Right.

DR. WINN-DEEN: Okay. It's in the back of the left hand section.

DR. TUCKSON: Right.

DR. WINN-DEEN: Assuming they were all stuffed the same way.

DR. TUCKSON: Thank you.

DR. : It's missing in some of our's.

DR. TUCKSON: We'll take a moment and we have—our crack staff actually has copies.

DR. : Now the recommendations that we have here don't match the yellow recommendations.

(Simultaneous discussion.)

DR. TUCKSON: That's exactly right. Okay. So let me just get everybody's attention so that we can get the explanation. The observation by several around the table is that there seems to be three versions that we have floating. So, Suzanne, just so you'll know the questions that people have, there is the yellow version in tab 4; there is the last two pages of the white handout, which seems different than the yellow; and then there are the new versions at the front of the—

DR. WINN-DEEN: They're totally new. It's not a new version.

DR. TUCKSON: It's a totally new deal.

DR. WINN-DEEN: The new recommendations.

DR. TUCKSON: So what people just sort of need is just a quick overview as to where we are in the process and which document we should be looking at.

MS. GOODWIN: The recommendations that are in your briefing books you don't need to use those at all during this meeting. I would work directly from the handouts in here and the recommendations that are lettered are brand new. You have not seen them yet. We're going to be reviewing them today.

DR. TUCKSON: Great. So is everybody sort of squared away? Are we all on the same page? We're going to be talking about the same stuff the same way. So the things that are the letters, for those of you who have made the observation who read ahead, who noticed that you haven't seen some of this language before, that's because you haven't seen it before.

(Laughter.)

And so that's what we're going to talk about, those letters. All right. So, with that, let me turn it back to our chairperson. So let us know where we're sort of launching in?

DR. WINN-DEEN: Okay. So we're going to focus on things related to FDA. The first one is the issue of companion diagnostics or co-development of tests, biomarkers, with the drug.

This was an area that was identified as a gap where we had not made any kind of a comment or recommendation at the previous meeting. We now have a straw man recommendation that there is a couple of things that we could potentially say.

(Slide.)

That's on this slide. And it's also in your handout. It's letter A with two options for straw man recommendations.

The first concern is whether FDA should continue to foster collaborative opportunities between the public and private sector to encourage this. Obviously, the Critical Path Initiative office is involved in that. There is the Office of Combined Products that could be working on that. The second option is whether we should ask FDA to continue to provide guidance to industry about best practices associated with co-development. Right now there is a white paper but not yet a guidance document from FDA.

I think we probably would like to see FDA complete that job as they, I think, already have in their plan but do we want to say something specifically in our report encouraging that?

So those are the two topics that are really up for discussion on this subject right now. I'd be happy to take any comments.

Debra?

DR. LEONARD: Can someone comment about how feasible it is to do this type of co-development? Since it seems like it may work logically for the target pharmacogenomics where you know the drug is useful for a particular target like herceptin, HER2neu or Gleevec, BCRabl, and then you would know what test you want to be doing. But if it's for adverse events or dosing or those kinds of things, how feasible is this to even think that you're going to get two of these coming out at the same time given how clinical trials work?

DR. GUTMAN: That was actually probably the most common criticism of the original concept paper was the notion that FDA was delusional in terms of mapping the two life cycles. We actually weren't. We were simply putting a target for the optimal way to do things and the out was the one advice that I would give to anyone developing this is you're absolutely right you can't always have development in parallel.

So it's absolutely critical when you're doing important parts of the second phase or the actual critical third phase of drug development, it's critical to get your hands on samples if possible, to get them in an unbiased manner if possible, and to store them in an analytically stable way if possible so that it may be the only chance to get material. So if it's a late stage discovery you can at least retrospectively perform prospective studies but I think it's a lot harder—it's a lot easier said than done.

So although I would agree with Dr. Woodcock's statement, I have a general perception that many drug companies are starting to get it and are starting to become more sensitive to this tension between the blockbuster drug and having a drug that works rather than one that hits the dust at the 11$^{th}$ hour but I still think it's easier said than done.

It's feasible in some cases. It's a scramble. HER2 is a perfect example of a place where we scrambled and we stood on our head and, contrary to popular belief, drugs and devices can work together and can actually sometimes retrieve and bail companies—bail products out. In some cases you can't. In some cases if you don't get the right data you never go back and you'll never have the evidence-base to make the product a success.

DR. WINN-DEEN: Steve, can I ask a question relating to what are the criteria that FDA is thinking it will use to determine if a drug requires a companion diagnostic? Are there some—is there some internal discussion of exactly how that determination is going to be made?

DR. GUTMAN: Well, I'll give you a first pass but then I'll pass it on to either Janet or Allen. I think we're learning. I think the whole issue of the voluntary genomic data submission is to start to get a feel for that. Our pre-IDE process is starting to get a feel for that. So I'm not actually sure we have all the answers for all the instances but Janet might have all the answers.

(Laughter.)

DR. WOODCOCK: Well, when you talk about require—okay, for FDA to require something it requires regulation or statute. Okay. Everything else is guidance. Right now drugs are required to be safe and effective. So we can't require something else unless it's necessary for the drug to be safe or

effective at this point.

So the answer is that we would require it where you couldn't rescue the drug any other way and if you can rescue it with safety or you can rescue it on getting a treatment effect up through a diagnostic then that would be a requirement for approval. Otherwise companies can try to get their drug on the market untargeted or without whatever safety diagnostic if the benefit/risk will fly. That may not be optimal, though, and the fourth hurdle may start intervening on this at the end of the day but at the moment those are the statutory and regulatory requirements and require some type of reg change to change that.

DR. EVANS: Can you just clarify? In the case of HER2neu, couldn't one make the case that in order to be effective you have to be over expressing HER2neu and, therefore, does that fall into the—

DR. WOODCOCK: Right. Well, that's a good example. In that case the company has presented publicly that they believe they'd still be studying the drug and they would have required 32,000 patients or some such thing in order to reach statistical significance and then if they got statistical significance in the whole population and got the drug approved probably no one would be willing to pay for it. So there were practical reasons that that was a much more efficient drug development program to do the targeted therapy. That doesn't mean that every single person who scores below a certain threshold on some tests by a laboratory doesn't respond to the drug. It means that you've enriched the population significantly by doing the test to the point where a drug development program was actually feasible with that drug.

So that I think we'll see more and more in the future as we move towards more narrowly targeted therapies. However, if, in fact, a company had chosen to do this very broad study of that drug or any other drug and had shown statistical significance and didn't have too many side effects of the drug, they might get it approved anyway but my point is, which I was trying to make earlier, is that would be a bad outcome for almost all parties. Even the company in that case.

DR. WINN-DEEN: So I guess it's really—right now it's centered on the pharma company to look at their data early on and make a decision about whether enrichment is going to be helpful to them in either the marketing or the approval process.

DR. WOODCOCK: Right. I want to say one more thing about this. Not only are we trying to get this guidance out, which is I need to like spend more effort on this but the C-Path Institute—it isn't like there is an unlimited number of targets out there that are being pursued right now and so FDA actually in cancer has looked at the most common targets and we're trying to work with the C-Path Institute to get the diagnostic companies—we had to get panels of assays and look at their performance, okay, so that instead of the pharmaceutical company trying privately to develop its own assay for its own product for some target that there could be panels of assays available that are still research assays but could be available because you don't know in advance what assay is actually going to be the most predictive of performance of a given product. Is it the gene sequence? Is it gene sequence, gene expression, et cetera, et cetera?

So anyway we're working on that because it isn't as if there's an unlimited number of targets that are being explored in any given time in any given field so there are probably some ways around this in the future.

DR. WINN-DEEN: Are the public-private partnerships three-way partnerships? Are they including both pharma and diagnostic companies or are they just including pharma?

DR. WOODCOCK: All diagnostics, yes.

DR. WINN-DEEN: Okay. So as the member from the diagnostic company, I can say this is the first I've heard of that opportunity so I would urge you to maybe work a little harder to get the word out on that to the—there's only a handful of people working in molecular diagnostics.

DR. GUTMAN: Yes, but there is an interest in making sure that the diagnostic interests are at the table, the staff people are cognitive of that and are making a deliberative effort, frankly, not to just tilt towards the big players but to get a representative section of the industry.

DR. WINN-DEEN: Kevin?

DR. FITZGERALD: I was just wondering. I realize that the situation we have here in the United States is somewhat unique but we don't operate in a vacuum. Are there different dynamics elsewhere in Europe say, for instance, with these kinds of questions? Are they coming at this with a different sort of set of criteria and how do we parallel with them?

DR. WOODCOCK: I could answer that if people are interested. Europe has—their dynamic is different, okay, as you pointed out and they are more pragmatic. Are you surprised with that? And they are very upset because due to, I think, the efforts of the NIH and FDA over several decades, much of pharmaceutical R&D and other kind of R&D has actually shifted into U.S. from Europe, which used to be the heart of it. And, therefore, they've come up with—I forget what it's called but European Innovation Initiative or something. They're going to put like of the realm of billions of Euros into something sort of like Critical Path where—but it's government funded—whereby industry and academic partners can apply to the commission, the research arm of the European Commission, for these grants, for development grants in various disease areas. So they will be trying to develop biomarkers and do things like that under this European initiative. It's just getting started, though, and again it's a grant type of funded activity so it's not clear how that will come out and what it will be targeted on but we, of course, are in touch with European regulators and the people at the commission and we'll be following that.

DR. WINN-DEEN: Francis?

DR. COLLINS: So again just to try to bring this particular discussion into practical example, HER2 was mentioned but a more recent one, and I'd be curious to see how this is playing out, would be the story of Iressa. So here we have a drug which had all kinds of promise targeting the EGFR kinase and yet at the same time when it's tried in lots of patients it looks as if the overall response doesn't look very impressive. In fact, FDA evaluating it was singularly unimpressed. At the very same moment a publication is coming out in The New England Journal and Science are pointing out that there is a subset of patients, maybe 15 percent, of European background and higher in Asian background that has specific mutations in the kinase domain that appear to have in some instances, many instances, really dramatic responses.

So where does that stand and what are the lessons from that where we have this sort of funny event where at the same time in the scientific community there's a huge buzz of excitement about this as a targeted drug for a subset of patients with disease that we previously we haven't had much to offer, namely lung cancer, at the same time we have the scenario of FDA deciding the drug doesn't seem to show efficacy overall?

So how could this go differently in this new era that we hope we're getting into?

DR. WOODCOCK: Well, I mean, that's the worst example of what we don't want to happen which is here we have a drug where many people know people who have had dramatic responses to Iressa but basically it is recommended not to be used because, first of all, Tarseva did show—which is very similar but showed a survival advantage, Iressa did not in a trial, and yet we have these small series, frankly, which I believe are small series, which lack enough validation probably to be broadly used that show you might be able to target Iressa.

So that to me shows the need and actually we are pursuing this so the need for developing panels of assays and having available—it's not like the EGFR is like some mystery target that nobody heard about before so the need to develop assays. We need to—the technology, though, at the same time don't forget Iressa was developed like over seven years or whatever. The technology has advanced and our ability to do these things has advanced, partly due to you and others, to the point where we can do things now that probably weren't conceived of a decade ago.

So, yes, there is—these oncology targets are one of the first things that we're working on to try and develop assays and panels of assays. Not de novo. Not as research projects but to bring together those diagnostic developers who have such assays, get them all at the table and develop in a consortial

manner and see if we can figure out some predictions.

DR. WINN-DEEN: Okay.

DR. WOODCOCK: In a way that would be acceptable to Steve and to the drugs people at FDA.

DR. WINN-DEEN: Reed, you had a comment?

DR. TUCKSON: I'll pass.

DR. WINN-DEEN: Okay. Debra?

DR. LEONARD: Well, just not to compartmentalize ourselves too much but the EGFR is covered by patents and no one can do the testing except for the patent holders who are enforcing, which is a major issue.

DR. WINN-DEEN: That's on the discussion for tomorrow.

DR. LEONARD: Yes.

(Laughter.)

DR. TUCKSON: Yes. But, by the way, would you make sure that we capture the connection between this and that? I don't want to lose that bridge. That's a very, very important bridge.

So let me make sure then that as somebody who doesn't do this every day that I understand the recommendation now and are we developing a consensus here of opinion. I think the challenge that I'm having on this as somebody from outside of this specific area, how do you—are we saying something about the role of FDA and government to facilitate the private sector manufacturers to be able to do something? I mean here it's-I'm not sure I understand the role of the FDA here. So it's kind of like it's hard to—maybe because of the words. The co-development word may be the problem for me.

DR. WINN-DEEN: Yes. I think part of it, Reed, as was pretty clearly stated in the Critical Path paper, is the FDA has the advantage of seeing everything.

DR. TUCKSON: Right.

DR. WINN-DEEN: Whereas, individual manufacturers see only what's in their little stove pipe.

DR. TUCKSON: Right.

DR. WINN-DEEN: So I think FDA does have a role here in terms of looking at patterns and saying, 'Oh, well, look. Tarseva and Iressa, they're both targeted to the same thing. Maybe the same kind of test might help improve…' just to keep on that example '…might improve the efficacy of both of those drugs.'

DR. TUCKSON: Okay.

DR. WINN-DEEN: So I think their ability to look crosswise is, I think, a very—

DR. TUCKSON: Right.

DR. WINN-DEEN: --they're in a unique position to do that.

DR. TUCKSON: Well, maybe what—and that's what I was hoping to hear. So what I think that we're—that what we might benefit from in the next iteration of this would be what is the problem we're trying to solve. What is the opportunity? In other words, so that—in other words, the American people will benefit from having more things to treat their particular condition if we were able to have this more broader approach. All the roads sort of coming together somewhere so that you can then stimulate and you extract maximum value out of the individual activities of individual companies and initiatives, to facilitate that, this is what needs to occur. I think if we sort of start to begin to think something along those kind of preamble lines so we can see how this lines up might be helpful for the next draft.

DR. WINN-DEEN: Okay. I am mindful that we have a number of issues to discuss so I just want to ask if there is any issues with going ahead and keeping these two sort of conceptual recommendations in here. One is to sort of reinforce FDA's initiatives in terms of trying to generate public-private partnerships to cross company lines and the other is to provide guidance that again benefits the whole industry in terms of—

DR. TUCKSON: I think the technical concern around the last one is just the word "guidance" and that that means legally from what Janet said.

DR. WINN-DEEN: Well, FDA has specific documents which they call guidance documents.

DR. TUCKSON: Okay.

DR. WOODCOCK: We are happy to try to do one and two.

DR. WINN-DEEN: Okay.

DR. WOODCOCK: Speaking for myself.

DR. WINN-DEEN: Okay. Agnes?

MS. MASNY: Do you think it would be helpful to get the white paper from the FDA for the committee members?

DR. WINN-DEEN: The companion diagnostics white paper? I think we've passed that around before.

MS. MASNY: You've thought about that. Okay.

DR. WINN-DEEN: But we certainly can resend.

MS. MASNY: Okay.

DR. WINN-DEEN: Okay. I'm going to move on then. The next issue was this whole concept of how does a test potentially guide drug dosing and what is the mechanism by which a test is ordered and then that result is translated into what the patient actually gets as a prescription.

Quite often the drug labels today contain information that a drug is metabolized in a certain way but it doesn't really provide any guidance to the physician about what to do about that. So we have tests like the AmpliChip from Roche that are approved but the physician still doesn't know what to do if they order the test. Even if they know that the drug is metabolized they're still missing that last piece of information.

So the issue is really how do you get to the point where you can provide good dosing recommendations to the physicians and you have the right interpretation algorithms for any kind of a pharmacogenetic test?

So we had a couple straw man recommendations and this is recommendations that are under "B". So our thinking on the committee is that this is primarily potentially a labeling issue so should the FDA provide or require the provision of dosing, translation of test results into dosing recommendations in a drug label? And what do you do about requiring that diagnostic tests perform at a certain accuracy level so that if a test is being used to guide dosing you actually have confidence in the test result so that when you do the dosing recommendation it's going to translate into good medicine, particularly if there's a drug that has a narrow therapeutic range or a high toxicity index?

Steven?

DR. TEUTSCH: One has to go even one step beyond that. We know that labels don't influence care very much. I know FDA has made some real strides to improve the labels but we need systems that help take it from the recommendations based on the quality of the data that come out of FDA and others to get it into care and get it in the hands of docs because simply putting it in the label—there's too much for labels and docs don't remember it. So we need to actually engage the health care system to develop appropriate systems for doing that. We see it with coumadin. We've known how to do that for years and we've had—and now we have coagulation clinics and when we get to the electronic health records and those kinds of things it needs to be built in there.

So I think we need to push. Yes, we need the good diagnostic information and we need to talk about the quality and all that sort of thing but then we've got to get the systems in place.

DR. WINN-DEEN: So do you think we need a third recommendation which is basically how do you translate something off of a drug label basically now into the practice of medicine? What kind of mechanisms are there to educate physicians to train them to—

DR. TEUTSCH: Well, you need the education so I think—

DR. WINN-DEEN: --have look up tables—

DR. TEUTSCH: --and that comes later but I do think you need to say it takes more than just

telling people. It takes systems change to make it happen and I do think we need a recommendation of that sort.

DR. WINN-DEEN: Okay. Andrea?

DR. FERREIRA-GONZALEZ: Well, maybe you can clarify this for me. I don't see—I don't understand very well the straw man recommendation. The first part is that the FDA should provide adequate information as part of their label. I guess the new part would be for both the drug and the diagnostic because aren't the FDA currently doing that, the recommendations already?

DR. WOODCOCK: Yes. I think under B-1 the issue is really having the data to put it in a label. Okay. It isn't like we would withhold data from the label if it actually existed in the real world but, just like we talked about with warfarin, we need information--or this codeine article that was just passed out, which basically shows that morphine analgesia isn't really very effective after tonsillectomy or whatever. We need outcome data to put in the label that tells the clinician if you do this, this will happen. If you do that—I mean just to say, well, this will—the blood levels will vary around—which is what is in there now. Clinicians are telling us that that's not very useful information because they don't know what it means for their individual patient for that to happen. Somebody has to do the study. And so again FDA doesn't have the ability to mandate such studies. We're trying to get these studies done through various consortial activities and so forth.

DR. WINN-DEEN: So is there another mechanism for that? I mean, I guess my question would be if you got a new drug application and it came in and it said, 'By the way, this drug is metabolized by 2D6.' Knowing what we know today, would you go back and say, 'Okay. With that kind of information we're going to require that you look at different genotypes of 2D6 and see if the same drug is effective and safe in people with low, medium and high metabolism.' Or is that outside of the purview of—and make dosing recommendations based on that?

DR. WOODCOCK: That would depend again, as I said earlier, on the therapeutic index of the drug and whether or not those types of genetic adjustments based on genotype were necessary for the safety and effectiveness. Companies right now—given the health care system, they're not going to want to put a drug on the market that says you have to modify dosing based on drug metabolism because most clinicians would have no idea what they're talking about. Okay.

So basically what companies are doing nowadays is avoiding developing drugs that have polymorphic metabolism. Okay. Which is probably, given the current situation, a very good idea. So we would—again just like targeted therapy, FDA would not do that unless it were absolutely necessary to modify the dosing for safety and effectiveness.

DR. WINN-DEEN: So in order to get dosing information it's really going to have to be voluntary dosing submissions from the pharmaceutical companies. Is that really the reality of where we are today?

DR. WOODCOCK: Well, there is a lot of drugs on the market that could benefit probably from pharmacogenetic directed dosing but, yes, there is no way to really mandate that from the FDA's standpoint. That's correct.

DR. LEONARD: Why not?

DR. WOODCOCK: Because the drugs are already safe and effective. They're on the market because they're safe and effective.

DR. LEONARD: I mean for new drug submissions. I mean the horse is out of the barn for all the drugs that we have out there that we know there are 15 to 20 drugs that have genetic variability included in their labels and there are no dosing recommendations for any of those 15 to 20 drugs.

DR. WOODCOCK: Right.

DR. LEONARD: Do we want to keep doing this with more and more and more drugs where we just keep putting them out there where there's genetic variability now included in the label and physicians don't know what to do with it? So if the FDA can't say, 'You know it's metabolized by 2D6, figure out

the dosing for the different 2D6 genotypes,' who else is going to ask for that?

DR. EVANS: But it sounds—I mean from what you're saying—the FDA's hands are tied because it's shown that it is safe and effective without looking at genotype. Now granted, of course, there are subtypes that would be safer or more effective but you guys can't mandate that. Right? I don't think the FDA is the answer to that.

DR. FERREIRA-GONZALEZ: How are you drawing the line now? For example, looking at re-labeling for the warfarin. What is the data that you need to make that trigger and could you ask for that in a prospective way?

DR. WOODCOCK: Okay. Well, say for warfarin we would need to know that using genotypes to direct dosing would probably result in some clinically significantly improved stabilization of the INR that you wouldn't have—that there was some clinical significance to doing—adjusting the dose ahead of time. Just like this study that was just passed out showed there would be very little clinical significance to adjusting codeine or deciding whether or not to use codeine based on your metabolism because morphine doesn't appear to work either as far as I can learn so it really doesn't matter. That appears to be the conclusion of the article and the data aren't presented in there on the pain correlations so it's really hard to say.

Anyway so we would have to—now Iressa, for example, we have made a recommendation, okay, that Iressa not be basically instituted in new patients. All right. Now if we could find a targeted solution that would identify people who responded to Iressa then that would be changed and so that would be an example. The same with drugs as they're being developed. That's how Herceptin, like we said earlier, got on the market basically is they pursued a strategy of targeting but for the vast majority of things that are kind of in this gray zone where we don't know how clinically significant the pharmacogenetic directed dosing would be, how much improvement it would cause, then it is very difficult for us.

DR. FITZGERALD: Could I just add on to Andrea's question because I don't think it quite got there? First of all, how are you currently designating something as safe and effective? With your push on personalized medicine, isn't that going to shift? Won't that raise the standard for safety and efficacy? The more we know, and I would presume that would have that kind of push up effect.

DR. WOODCOCK: Eventually it will. As we develop more targeted therapies, the treatment effects of those therapies will be larger. The benefit will be larger and that's true with some of the therapies we have now. They are directed that way. Therefore, when you have to compare new therapies against that—let's take the best example, which is the—which is HIV drugs. All right. Those are actually personalized against the virus so that whatever virus you have, whatever its mutations, you get a drug that is targeted to that.

Nowadays you can't just develop a drug and say it should be used in all HIV patients anymore. So the bar has effectively been raised that you have to target those therapies and you have to know what they're useful against and so forth, and that could occur in other fields gradually as more effective therapy. But that's assuming that you're getting a therapy on the market that's actually more effective because it's targeted but that is starting to occur. I think that will occur in cancer and that will occur in HIV and in areas like that.

DR. WINN-DEEN: Francis and then Jim?

DR. COLLINS: So in terms of the standard of proof for the efficacy of pharmacogenomics as predicting a good response, a good risk/benefit ratio, has FDA arrived at a conclusion about whether that can be based on retrospective data or whether it always requires a prospective trial? Because obviously warfarin is a very, very nice example here because there is retrospective data from warfarin on several studies to show you that if you go back and look at adverse events, major bleeds, they do correlate with the individuals who are in the category that you would predict, namely the slow metabolizers who then get toxic doses early on in the effort to try to adjust the dose. So one could say why isn't that good enough?

Now, I certainly agree if this is the poster child for clinical trials, I think most companies are collecting DNA and most companies are hoping if the drug looks like it's not going to quite make it overall that they can rescue it in that Phase III trial by identifying a subgroup that did show a response but then you'll be in that same category of asking would that hold up in a prospective trial and will FDA expect that to be shown before you would get to the point of saying, okay, it is a requirement to have this diagnostic done in association with prescribing that drug. So is there a policy decision that has already been arrived at here or is this case by case or how are you going to make a distinction between requiring prospective in some cases and not in others?

DR. WOODCOCK: Yes. Generally speaking, we want one—we want a hypothesis driven demonstration. Whether that is another retrospective dataset might be okay but we certainly don't want it out of a dataset that generated the hypothesis.

DR. COLLINS: That could be a bit circular.

DR. WOODCOCK: Yes. But with warfarin—I mean, I've heard from the insurers people are not going to believe it. There is really a fourth hurdle here that is very significant. First of all, we don't non-acceptance of something that's going to be very useful and, therefore, it's almost incumbent upon us to show the utility, the benefit to patients, retrospectively in a way that will convince clinicians.

If I'm taking too much time like beat up on me or something but—and then—so secondly we've got to convince the clinicians that this is—and the insurers that this is actually real and that it's valuable. So outside of the real technical point which is not using your training set to verify your results there is a real proof of concept here that's going to have to occur. If you ask me, I'm a believer in blood levels because I have approved like 400 generic drugs in the last several years based on blood levels. All right. But that doesn't mean that it's always clinically significant, I think, as the codeine example shows.

DR. EVANS: Francis basically asked my question. I guess the thing that I would again get back to is that in a way FDA is a prisoner of what data are out there and you can't mandate, it doesn't sound like, the requirement for collecting certain data unless there are already studies out there in a certain field with a certain class of drugs, et cetera, that say this is important for--especially for adverse reactions, right, where this—am I correct?

DR. WOODCOCK: Well, as a field progresses, once we have some proof of concept that a certain type of test or targeting or safety test is important either for safety or effectiveness then we can start mandating it because, as you said, there's a comparison out there of something to refer to. Like the HIV example. But when it's simply a hypothesis we cannot generate a requirement, a new requirement for drug approval in the United States that you do this, that and the other thing when it's only a possibility that it may improve performance.

MS. C. CHEN: So I know for a drug to be approved there's a Phase I, Phase II and Phase III trial. For Phase I to look at the effectiveness of the drug and then Phase II and Phase III to look at the safety of the drug. How do you know the safety of the drug by—and its effectiveness is actually—is being metabolized and is not being—how do you know it's really working?

DR. WOODCOCK: Actually in the Phase III trials usually there's a formal test of effectiveness. Usually twice, two trials. And so that's how you know it works. It's empirical. People are randomized to get the drug or get something else and then a statistical comparison is made. So that's how the drug is proven to be effective and that is a statistical test using p value and that doesn't use any pharmacogenetic adjustment.

MS. C. CHEN: How come you don't do that? Look at how it's being metabolized or how it's being—look at—for example, if a cancer drug is being used to see if it is truly shrinkage or some other kind of data like that?

DR. WOODCOCK: Well, we have inherited the technologies that have been available to us over time and what we're talking about now is a change as we have new technologies that we can use but we don't quite know how to use them yet. So we're doing the best we can under the circumstances, I think,

is the best answer we have. We have really advanced the treatment of cancer and many, many people are cured of cancer treated who weren't before but we can do better in the future and that's—we just need to figure out the pathway.

DR. WINN-DEEN: So I wanted to follow up a little bit on the discussion of beyond FDA what do we need to do to move it from—even if it was in the drug label to actually move it into clinical practice. Is this working through the clinical practice standards at various physician subgroups, create—do we have any thoughts on any other areas that either CMS or AHRQ that might within HHS be able to sort of move the practice of medicine part of it forward?

Steve?

DR. TEUTSCH: Let me elaborate since I sort of brought that up because I'm completely—assuming that you have a good diagnostic, you've got a good drug, and somehow they work together. Normally what we look for then is to apply evidence based medicine techniques. AHRQ is helping us with that through a variety of measures of evidence review so that we begin to understand what it is we do know and have sufficient evidence for on which we can then develop some guidelines. The guidelines are not generally developed by AHRQ but by professional and other organizations, and to some extent here at NIH and CDC, that then form the basis for saying, okay, this is what we think you should do and have some standards for clinical guidance that can then be translated into practice in a variety of ways.

I gave you a couple of examples of those but eventually, aside from health system kind of changes, you're really talking in the realm of quality improvement and that quality improvement agenda is very broad from anything from reimbursement kinds of things to specialty clinics, organization of care to pay for performance, a whole range of things that you can then begin to try and drive it into the real world of practice.

Clearly we're learning a lot about how all that goes but the government plays a major leadership role in multiple agencies in accomplishing that. With the health information infrastructure that we hope will be here that will try to come in parallel that will help us drive it and get the right kinds of metrics. We have surveillance systems then to monitor that this happens so there's a variety of ways but it's a very comprehensive effort.

I think the point is that the science gets you so far but you then have to have very active processes to drive it into care. The most sophisticated practitioners don't need this but the bulk of practitioners and systems do.

DR. WOODCOCK: I could say something. I'm going to have to leave but we have recently changed the drug label and we have issued an organized drug label with a highlight section that has the most important prescribing information in it. The importance about this is it is intended to be used in e-prescribing systems and it has computable readable--computer readable sections in it and we have established a repository at the National Library of Medicine and the FDA is committed. By the end of the year we should have the drug labels all up in the repository and then they will have real time changes so when the FDA approves a change in the label it will go right into the repository that day or the next day and have the real time information.

What we're hoping is that the electronic prescribing vendors as e-prescribing becomes more prevalent, they'll be able to incorporate any kind of pharmacogenomic dosing recommendations directly into that e-prescribing loop so there'll be a systems approach to incorporating that kind of information that could give doctors some signal when they try to prescribe a drug that needed that kind of adjustment in dosing because our experience as well is that label changes in the traditional ways of physician education are not effective in changing prescribing habits, period, and that we have to use-we're going to have to use other mechanisms.

Thank you all very much. I'm sorry I have to leave this fascinating discussion.

DR. WINN-DEEN: Thank you for giving us so much of your time today.

DR. TUCKSON: Thank you.

DR. WINN-DEEN: Okay. Are there other comments anybody wants to make about moving pharmacogenetics into drug dosing into practice of medicine? All right.

Let's go on to the next area which was adverse event monitoring. This was the previous recommendation from our discussion in March basically on trying to provide guidance on what factors would trigger labeling changes, which, I guess, I guess was part of the discussion we just sort of tried to have with Janet about is there any set of information or metric that if there's more than X percent of severe adverse events that's the death knell for a drug. Is there any specific guidance that FDA gives out on that or is it really still on a case-by-case basis?

I don't know, Steve, if you're the right person.

DR. GUTMAN: Well, again, I don't represent drugs. Allen does. But as I understand it, it is on a case-by-case basis and it is driven by the relative risk versus benefit. So if you think—I'm just not—I'm not sure that there's a single model that fits all drug profiles.

DR. WINN-DEEN: Allen, did you want to add something?

DR. RUDMAN: I don't know. I think it's really case-by-case. It really depends on the therapeutic area. Some drugs—past drugs, in particular, are dosed almost to toxicity and so you see high levels of adverse events and that's to maintain the efficacy at a high enough levels. Others are not. I mean, in other cases where you may have small adverse—small numbers of adverse events may be sufficient so it's really a case-by-case and to a certain extent it's based on the therapeutic area.

DR. WINN-DEEN: So would you have that discussion more in the private conversations that you have with a pharma company during the submission of the data from various phases? Is that where you would have that discussion rather than issuing a general guidance to industry so to speak?

DR. RUDMAN: Some of it is that and some of it is whether there are alternative therapies presently available. Would you accept a drug that had a much worse level of adverse events when something else is on the market currently? Probably not unless you could show a very good reason. So it depends to a certain extent on the drug but it also depends on the area that it's in. CDER is basically oriented towards the therapeutic area so you have an Office of Cancer or Oncology, given offices, and I think some of that represents those changes--those therapeutic differences.

DR. WINN-DEEN: Kevin?

DR. FITZGERALD: Just a quick question. When you do measure adverse events, how do you balance a large quantity of mild events versus a small number of severe events?

DR. RUDMAN: Not being a physician myself, I think I would leave that to the physicians to answer.

DR. WINN-DEEN: Any other comments people want to make on this area?

(Slide.)

Okay. Let's move on to one of Steve's favorite topics, oversight of home brew pharmacogenetic tests. So we heard from Judy Yost this morning about how things will be provided with or all assays are provided with a certain level of oversight through the CLIA process. Obviously FDA regulates kitted tests but so far has declined to regulate home brew.

So the questions are really whether we should—whether we feel there is a need for the Secretary to find a more effective mechanism for oversight of home brew genetic tests as opposed to any other kind of home brew tests. Are genetic tests exceptional or should we make this a broad recommendation since such a high proportion of genetic tests are done in the home brew?

Option two, which I think has already been asked and answered, was whether the Secretary should clarify whether FDA has statutory authority to regulate home brew. Which I think you guys already went through a legal analysis on that if I'm not mistaken, Steve.

DR. GUTMAN: Yes, I think that recommendation still is a fair recommendation.

DR. WINN-DEEN: Okay.

DR. GUTMAN: Because I'm not sure that the agency has actually made a clear public statement

about that so I don't have any objection at all to having that left on and having that perhaps made more clear.

DR. TUCKSON: Can we just, again for the new team at the table, restate what that is again? Just a summary of what is the rule and what is the status.

DR. WINN-DEEN: Right now home brew is regulated solely under CLIA and not—

DR. GUTMAN: Yes, that is correct. Right now home brew is regulated solely under CLIA. FDA has in the past, certainly the previous committee had suggested that it might be willing to—you have to be careful what you wish for so the idea that we would actually start regulating all home brew tests is probably a little—is delusional but the possibility of regulating some home brew tests might be—

DR. TUCKSON: Can we summarize—I'm sorry. Just one other summary just to make sure. Again has the committee—has our committee, just summarizing, reached an opinion about the adequacy of CLIA oversight of the home brew? I mean, given that it's—we're clearly aware that FDA isn't doing it but only under CLIA. Is there now—have we made a shared assumption about the adequacy of the CLIA oversight?

DR. LEONARD: Before I have a heart attack—

(Laughter.)

--and it's not about this regulation because I think this is a justified discussion but could we please not call these tests home brew tests? I don't work out of my home. I don't brew anything and it's really denigrating to the laboratories who do these tests.

DR. TUCKSON: What's a better term?

DR. LEONARD: Laboratory developed diagnostic tests.

DR. WINN-DEEN: Laboratory developed test.

DR. LEONARD: You can put in parentheses that it's also called home brew tests because there is a history of that but it's—

DR. TUCKSON: That's important.

DR. LEONARD: --it really—they should be called laboratory developed tests because they are developed under CLIA regulations and in New York State, at least, we have to go through a whole New York State approval and review process, which is very much similar to probably what the FDA would implement.

DR. TUCKSON: Right.

DR. LEONARD: So I just—I have a heart attack about this term.

DR. TUCKSON: No, that's important. That's important.

DR. FERREIRA-GONZALEZ: I'm with her--

DR. TUCKSON: That is important.

DR. FERREIRA-GONZALEZ: --because I'll have another heart attack, too.

DR. TUCKSON: I think it's important so we will ban that term.

DR. FERREIRA-GONZALEZ: I mean it's just not made out of the laboratory. There are reagents that actually have to be listed with the FDA that are used in these laboratories.

DR. TUCKSON: Right. So all I'm trying to do is I just want to make sure that I understand, and everybody is operating from the same page, especially since we have so many new folks on the committee that we all understand, have we agreed that the issue—that there is an issue here and that there is an inadequate oversight of these laboratory developed tests? So that we just—I'm just trying to get the background straight for the discussion.

DR. WINN-DEEN: I don't think we've had a specific discussion on that so I can't say that we have agreed to that at all. It's an issue that just keeps rising to the surface. I know a lot of laboratories developing tests that feel they are doing quite a good job and I'm sure this is like everything else. It's the bad apples that you have to be concerned about and not the majority of good apples in the barrel. So we can have a little discussion on that.

I know Francis is very anxious to say something.

So let's have a short discussion on point A or point 1, whatever here, do we even want to make recommendation number one and raise that issue again?

Francis?

DR. COLLINS: Again, just a little bit of history because this topic has been discussed now for ten years, beginning with the genetic testing task force of the ELSI working group, that Tony Holtzman led, which because of its recommendation specifically that FDA should take responsibility for oversight of these in-house tests led, in part, to the creation of the SACGT because that was one of the concerns that here was a group making a recommendation that would have an effect on HHS agencies but they were not necessarily placed in the right part in the government to be able to do so.

So the very existence of your prior committee, the SACGT, and potentially, therefore, of SACGHS tracks to this very issue. SACGT, once they came into existence, did an extensive amount of consideration of this and at that point the legal opinion was that FDA had statutory authority to oversee in-house testing. That has subsequently been questioned whether that was the right interpretation but it was the interpretation back in the late 1990s and SACGT did, in fact, spend a lot of their time on this issue and made some specific recommendations about getting FDA involved.

Again, just to clarify, CLIA oversight is a wonderful way to be able to make sure that a test is being conducted with appropriate attention to analytical validity that if you did the test and it said that nucleotide was a T that it really was a T but CLIA oversight does not, in general, extend to clinical validity or clinical utility, areas where I think many people were concerned about genetic tests not being implemented in a broad way in the practice of medicine without some indication it was actually giving you information that was useful and, better yet, information that was going to improve the practice of care. There, I think, FDA's involvement was considered to be essential if there was going to be government oversight. Just a bit of context.

DR. WINN-DEEN: So, Francis, do you think it might be more useful for option one to really talk about in the context of pharmacogenetics where you're going to drive a drug, either giving it or not giving it or giving it at a certain dose, that this is a place where you really need to have that tie in on the clinical validity made before it's introduced into clinical service? So maybe from that point of view this is an area where somehow we need to raise the bar a little bit over a generic laboratory test which has basically moved from research to the laboratory and has good analytical performance but doesn't necessarily still have that tie in to so what, you know, what are you going to do with that test result.

Debra?

DR. LEONARD: I don't know that we should emphasize this for just pharmacogenetic tests because you can have a BRCA1 result and a patient can have a mastectomy based on that BRCA1 or BRCA2 and that's not regulated by FDA either. Basically what Francis is getting at and what SACGT got at was that there's a gap in that FDA does pre-market review but not of laboratory developed tests, and CLIA really is for post market quality assurance/quality control once the test is up and running. So there's really this gap in laboratory developed test review before it goes live in the marketplace, if you will.

So I think that's the gap and I hope no one is behind me from the laboratories because they're going to shoot me in the back but it is a real gap that exists and I think part of the legal question that FDA asked after doing a lot of work in developing a review template of how they would review these tests, et cetera, was that this falls into the domain of medical practice, which FDA does not regulate.

So there is a lot of history here to this issue but it still remains a gap and I think it's something for SACGHS to consider if there is a good way of doing this but I don't think it should be done as a—it's needed specifically for pharmacogenetic tests because there are a lot of other laboratory developed tests out there for which medical decisions are made. If we're going to do it, we should consider it for the whole barrel and not just one pickle.

(Laughter.)

I'm sorry for the metaphor but it wasn't numbers or letters.

DR. WINN-DEEN: Okay. Any more lively discussion?

Okay. I think the task force can take those comments and we certainly will change the label on these recommendations. So it's my understanding that the group is okay with option number two, which is the clarification of FDA in a formal way, and we need to consider how option one really is not just related to just pharmacogenetics.

DR. : Is the only option going to congress for two? I mean, is that really the only way to do this?

DR. WINN-DEEN: Well, you have—either they have statutory authority or they don't and if they need it they have to go to congress. I think that was the thinking there.

Suzanne?

MS. GOODWIN: I just wanted to ask the committee whether they would prefer to take this recommendation out of the context of pharmacogenomics and consider it as a separate issue or would you like to keep, I guess, option one on the table for discussion as part of pharmacogenomics?

DR. FITZGERALD: On that note, what did actually happen before with SACGT on this and then do we build on that or do we use this as sort of a wedge issue to get at it?

DR. WINN-DEEN: A lot of discussion, not much in the way of answers.

DR. COLLINS: No, there was a very specific recommendation. We can pull that back up and circulate this to SACGHS. Basically, though, it did not get acted upon until the change in interpretation of the statutory authority became the issue. SACGT went away and it sort of is hanging in the air even now after all those years. So I think it would be very useful, since we never did get a formal opinion about the legal statutory authority question, to ask for that. And I appreciate Steve saying also that that would be a good thing.

DR. TUCKSON: We are going to circulate as we have periodic discussion with Judy Yost those pertinent documents from the previous committee.

DR. FERREIRA-GONZALEZ: We had a presentation this morning from Judy Yost for the notice of proposed rule making for strengthening or changing genetic testing. Will this gap be addressed in that notice of proposed rule making? That's something that we can ask CMS to further elaborate on.

MS. CARR: In the CLIA?

DR. LEONARD: If you look—there are clinical utility—it describes six steps of—

DR. FERREIRA-GONZALEZ: Yes.

DR. LEONARD: If you look at Joe Boone's presentation that wasn't presented that's the previous notice of intent.

DR. FERREIRA-GONZALEZ: Yes.

DR. LEONARD: Now what ends up in the final version that's going through CMS and everybody else now, I don't know what that will be but there is some oversight of how—I don't know if it's enough.

DR. COLLINS: But Judy specifically said that one of the issues was that CLIA doesn't really have authority over clinical utility and validity so I suspect she was signaling, if I could guess, that that's one of those areas where when the dust all settles, they're not going to be able to do a whole lot.

DR. WINN-DEEN: So maybe all we can do is frame the issue for the Secretary and basically say the gap is in oversight of lab developed test the issue of clinical validity and utility. We feel that there should be some bar in place for those issues but currently it doesn't appear that any of his agencies are responsible for identifying what that bar is or enforcing it. So maybe the recommendation just is that within HHS we should think about what agency might be best equipped to take that on and make that part of the process. I mean if we're really concerned about the quality of lab developed tests that obviously is an issue and from a level playing field issue it's one of the key problems that diagnostic companies have

with making a decision to take a test into a kit format because it has a significantly higher bar when you do that and you have to show a lot more things than you do if you just put it together in your laboratory.

DR. LEONARD: We may want to suggest that there could be some advance on the learning curve, if you will. New York State has had ten years or so of experience of reviewing these tests and, believe me, when they started they were not efficient. There were long delays. People would put them on the market before they even—or put them into use before they even got the review. Now the reviews are quite timely and within six weeks or so you get a response back. The comments are usually reasonable. You respond to those.

So they have worked out some level of mechanism for doing this at least for the New York State laboratories that seems to work and it would be nice if whoever you're going to ask to do this would not have to go through that same learning curve for all the other laboratories in all the other states.

DR. WINN-DEEN: We could just require all labs to get certified by New York State and that would solve the problem.

DR. TUCKSON: Just so we can move along, can we summarize again where we are with our understanding of option one and option two on this issue? What did we just agree to?

DR. WINN-DEEN: I think what we agreed to is that under option one we maybe want to clarify that the oversight issue is not just generic oversight but particularly the issues of clinical validity and utility being established before—

DR. LEONARD: Isn't it more pre-market review and approval? And that's going to be whatever criteria—there's more that goes into that than clinical validity and utility.

DR. WINN-DEEN: Right.

DR. LEONARD: So it's really pre-market review that's missing. There is no pre-market review of laboratory developed tests and that's the gap that we need filled because CLIA provides the oversight after they are up and running.

DR. WINN-DEEN: Right.

DR. TUCKSON: Let's see. I think I'm just trying to look at the folks' faces around the table. So I think somebody needs to say whether or not—is that a consensus or not? Is there a consensus that it's just the pre-market side and not the post approval side?

DR. WINN-DEEN: I think pre-market brings into the, you know, why are you doing this test at all issue. Whereas the post market is are you continuing to do the test in a way that is safe and effective basically. Is the test performing adequately? And that, I think, we feel is reasonably regulated under CLIA. The question is just the whole why are you offering it at all.

DR. TUCKSON: Okay. That's good. Then option two? Are we also—what is our recommendation? Are we accepting that recommendation, Emily?

DR. WINN-DEEN: Well, I think we definitely got consensus that we should ask the Secretary to clarify. I'm not sure if we got consensus on the dependent clause about whether we should go to congress to close the gap or not. I think it's a one-two thing. We need to first analyze whether they actually have the authority but the remedy I'm aware of, if we feel it's important, is to change the law.

DR. TUCKSON: If it's important enough to ask, is it important enough to do something about and, if it's not worth doing something about, why ask?

DR. LEONARD: Well, I think the question is, is the FDA the regulatory agency to take this on? So that's really the question. We know there's a gap. Should the agencies get together and figure out who is the best? Is it CLIA that should do that or is it FDA? I mean whose charge has to be changed?

DR. WINN-DEEN: Before you go to congress you're saying?

DR. LEONARD: Yes.

DR. WINN-DEEN: Yes.

DR. COLLINS: I guess, I would challenge whether, in fact, CLIA could take on this pre-market role without a change in the legislation.

DR. LEONARD: No, I don't mean without a change. We're specifying FDA here. Whoever is charged—I mean, maybe we don't want to be that specific but HHS may want to get together with all the agencies and figure out which agencies they want congress to be giving the authorization to do this rather than us saying FDA because FDA says they don't have the resources either.

DR. COLLINS: Well, the option as currently stated that seems to leave that open. Should encourage congress to pass legislation closing this gap without necessarily saying how it should be closed. Is that what you're arguing for? We should be clear about that?

DR. LEONARD: Well, maybe you want to ask whether any of the agencies have statutory authority, not just—I mean—

DR. WINN-DEEN: Whether HHS.

DR. LEONARD: Yes. So I mean maybe we want to broaden this because it does seem that the way this is stated that they're going to look at whether FDA does and, if it doesn't, then give it to them. Whereas, we may want to be more open than that. I don't know. If HHS is happy with FDA doing it that's great but maybe you want to have that discussion.

MS. CARR: SACGT did, as Francis mentioned, look into this very closely and the committee didn't identify any other agency besides FDA whose statutory authority seemed to encompass the pre-market review of laboratory developed tests. So that might—unless something has changed since the 2000 report of that committee, I would think that we might want to accept that analysis and then maybe Steve could suggest how—if the committee were in agreement—how we might get a sense from either HHS or FDA specifically about the current opinion, legal opinion within the agency and the department about whether you do or don't have that authority.

DR. GUTMAN: Yes. I think getting clarity is a good idea. I don't at all object to being—Debra, of course, is the world's expert on thinking outside of the box so I certainly don't personally have any opposition to any creative way of addressing the parity issue and FDA, as you'll recall, when we—and maybe you won't recall but when we were addressing this under SACGT was trying—actually with SACGT's help—to develop a risk-based approach in which we would establish more control over certain tests and less control over other tests and we were actually working—actually one of the niduses of the template—and Dr. Leonard is actually a heroine here since she was very involved in helping us craft the template that we use in our review every day. Every product now cleared in America is based on a template that a working group of professionals helped craft but the deal was that we were talking about all kinds of alternative communication efforts that would be non-intrusive that would be least burdensome and that would be most revealing so that people would actually understand what was going on but that wouldn't involve us. Obviously if we were resourced and got 1,000 new people we could go out and duplicate everything CLIA does. We actually didn't really have that in mind.

DR. TUCKSON: Let me just make sure that—just to move us along. I think that dichotomy—the decision point here is—I think as I understand where Debra is taking us and what we just heard from Steve--is that we are recommending that the Secretary clarify whether FDA has statutory authority to regulate these laboratory initiated tests and if it does not for HHS to determine which agency ought to do it and seek the necessary authority from congress to allow them to do it. I mean that's what I hear you all agreeing to. Do I miss anything there? Done.

Next?

(Laughter.)

DR. WINN-DEEN: Okay. We have not too much time before our lunch break so I just want to raise this issue. We'll have the beginnings of our discussion on it but I'm going to cut us off so we can break at the right time for the people particularly who are on the webcast so that we keep our outflow on a timely schedule.

(Slide.)

So the issue that has been identified, and I know that a lot of people are aware of this, is that

there's two different human subject protection regulations. One is the HHS Common Rule, which governs most of the clinical studies done through NIH funded grant kind of mechanisms. And then there is the FDA Title 21 which governs clinical trials done in preparation for an FDA submission.

There has been some discussion in the community that some of the things that we would like to see happen in terms of public-private partnerships are going to happen partially in academia, partially with pharma companies. Pharma companies might want to use that data as part of an updated submission to FDA. And this issue that there are inconsistencies between these two regulations on human subject protection causes some difficulty in actually designing a study that could be used for both purposes. Obviously if we're going to fund studies, you'd like them to be able to be used not just for academic reporting but potentially also to change the practice of medicine.

So the FDA has issued a guidance recently on their interpretation of how one can use left over human specimens for studies that will be intended for FDA but there are still some inconsistencies.

(Slide.)

So I think what the task force is thinking is that in terms of trying to move this field forward it would be good to try and harmonize these two rules which I think are basically intended for the same purpose, which is to protect the rights of the people participating in studies but to encourage OHRP and FDA to somehow come together and harmonize so that there is one HHS set of rules to follow for all clinical studies.

Maybe Steve can give us a little update on what you know about where that process is already?

DR. GUTMAN: Yes. Well, obviously, we have, as you pointed out, tried to put out a guidance that would at least remove some of the pressure in what is clearly very distinct. We actually have a law that feeds into a regulation that I think the nidus may actually be deliberate, the notion that there are different motives in commercialization versus basic research. But there is so much of a gray zone that it's very hard for us actually to understand what drives those differences.

It's easier said than done. We would have done in it, in part, because actually the two approaches are being fed by separate—in our case by separate law and reg and in the case of NIH the Common Rule is driven off of regs. I do think there's an opportunity for us to harmonize and we do intend to and a request from this committee to do that can only encourage us to try and do that faster.

DR. WINN-DEEN: Mike, do you want to say something on the OHRP side?

DR. CAROME: I would just make several points. The issue of harmonization has been talked about for 20 plus years, I think, between OHRP and its predecessor, OPRR, and the FDA. So it has been a constant focus of the department with respect to that.

When the Common—I'd also note that the Common Rule is not an HHS regulation. It's a regulation promulgated by 16 or 17 different federal departments and agencies, including DOD, Veterans Affairs, in addition to HHS. And so that's important because if a recommendation was to change something in the Common Rule in order to bring about harmonization that would require negotiation with approximately 17 different departments and agencies. It's difficult enough having one agency alone promulgate a regulation on its own behalf. Getting 17 agencies to agree on a single set of regulations and changing those regulations can be very complex.

Regarding the issue of lack of harmony or inconsistency or conflict, it's important to analyze where is the inconsistency coming from and there could be three possible levels. One is at the level of the words used in the regulations, the actual text. I would assert that there is little substantive difference between the two sets of regulations we're talking about to say that that is the source of the problem, although if someone wants to challenge that assertion it would be helpful for someone to specify where is the regulatory language differing that's causing the issues and the concerns.

The second level where inconsistency can result is on guidance and interpretation of the regulatory language. Certainly where you have the exact same language, if it's interpreted differently that can obviously result in problems. And we strive when we are talking about the same language not to

have differing interpretations of the exact same language, particularly within our own agencies.

The last area of possible inconsistency is at the level of institutions and IRBs that implement the regulations. IRBs and institutions may be misinterpreting the regulation or think there are differences that are substantive where there are not and that may lead to problems with consistent implementation of the regulations.

Is this the issue being raised unique to pharmacogenetics? My sense is it's not but if there is some unique issue and are viewed with inconsistency with respect to this area of science it would be helpful for you to specify what that is in any subsequent final report so that the agencies understand where the issue is but my sense is that this is not a unique issue to this field of medicine and research.

DR. WINN-DEEN: So is it your belief that a study could be designed with human subject protections that would meet both the needs of the Common Rule and the FDA guidance so that they're not in conflict with one another? I guess that's my main concern is whether this is making it so that a study has to be designed as either an academic study or an FDA directed study and not one that could be used for both purposes.

DR. CAROME: I think with the current regulatory language one can do studies that satisfy both sets of regulations again because I don't think there's any—when you say conflict, I don't think there's language that says FDA regulations say A and that is in opposition to the regulations in the Common Rule. I don't think there is such dramatic differences.

For twenty years research has been done in multi-center, large clinical trials, all sorts of research have been done in which people are subject to—the researchers are subject to both sets of regulations and compliance has not been a problem. I don't see this field of pharmacogenetics as being—having—raising unique issues that we've not been faced with for many years.

DR. WINN-DEEN: Steve?

DR. GUTMAN: Yes. I actually believe that the problem is greater outside of pharmacogenetics than it is for this because in the pharmacogenetics when you are doing drug studies you're probably already getting informed consent and it wouldn't take very much crafting to figure out how to get IRBs in informed consents to create something that covers everything.

So I think it's exactly the opposite. I think that problem is in areas where there isn't informed consent where people are going into laboratories. It's a very common practice. Certainly when I was in a lab and doing either quality assurance or research work it was a very common practice to take samples that are left over to de-anonymize them to take minimum demographic information using everything from quality controlling your instrument systems to doing some method study to doing some basic research.

Under FDA law there is this odd—the law itself allows informed consent to be waived only in a crisis emergency situation and then there's a reg that says that a sample is a human. So, theoretically, you can't do what we've done for—well, for 20 or 30 years. You can't go and take a sample about to be thrown out, rip off the label, de-anonymize it, and then use it for research purposes. You have to find the patient. If the patient is dead, you're off the hook. Otherwise you need consent and that some people find noisome.

So we created an enforcement discretion guidance document that suggested we get a life and we lighten up a little bit and that we didn't see patient safety being compromised if you ripped off the label if the sample had been used for routine clinical purposes and was about to be thrown out anyway. We did see some benefit to promote the critical path.

We actually have an obligation with or without this committee's recommendation to codify that in a modification to the reg. We can't just rest that on the guidance. So it's our plan to develop a reg.

So from my perspective this isn't hurtful or harmful. It might be helpful if it might encourage us to try and prioritize this higher because we are--like Judy felt very defensive when she presented what have we been doing all this time. Well, we do have a day job and she has a day job. So I could easily see this—if it's fixed and it's not creating a problem for industry, I could see this being something we

wouldn't put at the top of our plate perhaps.

DR. WINN-DEEN: Do you think it would be most helpful for us to make a different kind of recommendation, which is that pharmacogenetic studies should be in their design and their informed consent, particularly in the design of how the study will obtain informed consent, should be mindful of both the FDA and the Common Rule requirements and try and make studies that have informed consent that is useful and—

DR. GUTMAN: That would be very wise to—

DR. WINN-DEEN: --required with both rather than trying to harmonize the regs to just say studies should consider both of these sort of issues. This is not my area of expertise.

DR. EVANS: Why does that just have special relevance to pharmacogenomics and not—I'm just kind of wondering why it's in here.

DR. WINN-DEEN: I think it's in here because of the translational aspects of if a study is done out in the academic community and it could actually be used potentially to change a drug label but if it wasn't done with the right FDA informed consent you can't submit it to FDA as part of a package to make a change. I think that's why it was in here, not that it's an exceptional area. Just that we need to be mindful in the translational medicine work that some of these things will have to go through FDA.

DR. TUCKSON: All right. A process check here. We're bleeding over into lunch. I think what we might want to do is if there are some comments that can be either focused to a consensus achieving statement or if there's—let's do those right now and people can contemplate them while they munch. If there are questions about the issue and you want to discuss the issue, I think we're going to have to wait until we come back after lunch. So just for those who had their hands up.

DR. TELFAIR: Well, actually that was going to be my question. It seemed to me that you've got—this is definitely not my area but from—if you're going to make the recommendations, it seems to me, with specifics, let's cut to the specifics because what has already been discussed seems like more than enough information even for someone like me that's outside that right now what we just need to do is just talk about specifically what it is we want to get. You started the recommendation in terms of refocusing it. It seemed to me that would make a big difference but also that whatever is done here as a recommendation will potentially influence something to move it forward. Just what would that be? I guess I would be open to hearing that but that's what my thinking is now. Can we just cut to it?

DR. WINN-DEEN: Debra?

DR. LEONARD: I was thinking it sounds more like what we need is a single document that says if you do this you've covered both. It's not really harmonization. It's really just simplifying it so that there's one document that says if you do these things then you've covered both FDA and Common Rule and maybe that's what's needed rather than some harmonization. Just a combined document.

DR. WINN-DEEN: I am going to let people think on that and we're going to take our lunch break.

DR. TUCKSON: The lunch—given that we're a little bit later, instead of convening at 1:30, we'll convene at 1:40 but we're going to start at 1:40 or, heaven help, we'll all be in deep trouble.

The other thing is that we'll start at 1:40 with public comment so those that are the public comment folk, be careful that you don't get trapped down in the cafeteria line and don't make it back because you'll lose your spot.

(Whereupon, at 12:53 p.m., a luncheon break was taken.)

* * * * *

A F T E R N O O N  S E S S I O N

DR. TUCKSON: Well, thank you all very much for returning for the afternoon session. We are very pleased that everybody made it back on time and those that didn't, they know who they are.

We take the public comment session very seriously and we're very glad that we have our public comment people. I need Sarah Carr.

DR. TELFAIR: Shouldn't that be turned off during public comment?

DR. TUCKSON: What's that?

DR. TELFAIR: The screen?

DR. TUCKSON: Oh! Yes, I guess it should be since it's not relevant for that. That's good.

Where's Sarah? I need my list of the public comment people. Here she is. Okay. So I always love it when I can get somebody. I got Sarah the first time. Public comment people? What's the name of the people? Oh, here they are. Great! She has ripped out the page. She's upset with me.

(Laughter.)

You want the list, here! Take the list!

(Laughter.)

Okay. John Corcoran?

By the way, we do—though, I'm joking because I wanted you to wake up after your postprandial paralysis but we do take public comment very seriously and we are very attentive and appreciative of that.

John Corcoran is from Export Management Systems, Incorporated.

Are you available? Hey! Could you go that way so that our next will be appropriate craned?

(Laughter.)

MR. CORCORAN: Should I use the mike?

DR. TUCKSON: You're cool. You need a mike. Thanks. Otherwise they won't get you onto the webcast.

**PUBLIC COMMENT**

MR. CORCORAN: Okay. Thank you very much for having me here today. Just for clarification, my name is John Corcoran. I'm from an organization called Examination Management Services, Incorporated. That's EMSI for short.

The purpose of my brief comments today is really to address two policy issues that we've identified particular to the large population study that is being considered.

The first is the need, of course, to gather data on a national basis with equal diversity across the spectrum of all the data points being collected.

The second is also to focus on the comfort and convenience of the participants of the study.

Very briefly, EMSI is a national organization who collects biospecimens as well as medical records across the country. We've been doing this for about 32 years or so, mainly supporting the insurance industry. In the past five, six years or so, we've supported a number of federally funded projects as well as commercialization projects for pharmaceutical companies.

We have a platform which is basically a hub and spoke program. We are based in Dallas, Texas. We radiated out through about 250 offices into the community to collect data from the study participants through the use of our 6,500 plus certified phlebotomists.

The value that we bring to studies is that we offer the study participants again the convenience and comfort of having specimen and other data points collected in their homes or places of employment. Also, if they are mobile, as we are a mobile nation, we can track them on a longitudinal bases from place to place as they move forward.

We are also the largest collector of medical records in the United States. We collect medical records for our insurance clients as well as for our epidemiology and commercialization project clients. We do this again through a centralized coordinated secure hub in Dallas, Texas, where we reach out to over hundreds of thousands of institutions and providers across the country.

Our purpose today is to make the committee aware of our services and also to make the committee aware of what we feel are very important issues, specifically again to the point of the comfort and convenience of the study participants.

I know my time is limited and I want to thank again the committee for the opportunity to talk today.

DR. TUCKSON: Thank you very much for taking the time to share with us today.

Any particular questions from the committee? Okay.

Thank you very much, sir.

MR. CORCORAN: Thank you.

DR. TUCKSON: Next with us is David—David, I'm going to say this but there's a tendency that people seem to have to disagree with my pronunciation of their names.

MR. MONGILLO: A politically correct person would say, "Oh, that's pretty close."

DR. TUCKSON: But I think it's—

MR. MONGILLO: It's a soft "g". I can say that.

DR. TUCKSON: All right. So let me—now you really put the pressure on me.

(Laughter.)

DR. TUCKSON: What does that mean? David Mongillo.

MR. MONGILLO: Mongillo. That's right.

DR. TUCKSON: I knew it all along.

MR. MONGILLO: Very good.

DR. TUCKSON: I think, by the way, unless I've got this wrong but you may well be with the American Clinical Laboratory Association.

MR. MONGILLO: That's correct, vice president for Policy and Medical Affairs with the American Clinical Laboratory Association. Let me also add the welcome to the new members and the ex officios to this very distinguished group. We're very pleased. ACLA is pleased to provide comments upon the need for genetic testing oversight.

ACLA is an association representing local, regional, national, both independent and hospital-based laboratories throughout the United States.

ACLA agrees that the oversight of genetic test services is an important topic for discussion as advances in genetics and genomics lead the development of new laboratory tests and services. These tests are often driven and increasingly driven by physician and patient desire for technologies that hold promise of improving health care outcomes. Genetic tests make significant contributions to individualized personal health care in that they can detect disease or disease risk before the onset of symptoms when intervention might be most effective and they can target specific therapy for these diseases that might make it more effective for the individual patients.

We want to make several inter-related points with regard to regulatory oversight of genetic testing. First, the clinical laboratory industry is one of the most highly regulated health care delivery sectors. You heard this morning from Judy Yost and she pointed out that all clinical laboratory services are regulated under the Clinical Laboratory Improvement Amendments of 1988, CLIA.

CLIA regulations include multiple requirements, both general and specific, for laboratory quality such as requirements for appropriate training of laboratory personnel, quality control programs and proficiency testing. All of these requirements apply to laboratories that perform genetic tests. Further, CLIA utilizes a commercially—I'm sorry. Further, CLIA regulations require that before introducing a new method or test that does not utilize a commercially available test kit, the laboratory must establish and document performance specifications of accuracy, precision, analytical sensitivity, analytical specificity, and they have the responsibility for the quality of those results for patient care, clinical patient care.

We believe all of these are essential parameters of quality and performance. Adherence to CLIA

is ensured by on site inspections every two years, either by a state agency or by a CMS representative. Penalties for noncompliance are severe and include the possibility of revocation of the laboratory's CLIA certificate, without which the laboratory cannot operate.

Secondly, ACLA wishes to emphasize the importance of making any regulatory changes related to genetic testing only after determining that such changes are focused on legitimate risks specifically related to genetic tests and that changes are realistic, targeted and effective to address such risks.

Third, it's critically important to keep in mind that genetic tests provide benefits today and promise great advances in the future in diagnosis, screening and patient monitoring. Any new regulation should not create undue burdens that will stifle innovation or restrict patient access to these valuable services.

In that regard, ACLA wishes to bring to the committee's attention a key issue that, if not carefully considered, will have significant negative consequences for laboratory operations and patient care. That's the question of how genetic tests will be defined for regulatory purposes and how that definition will affect any specific new regulatory requirements.

ACLA is concerned that an overly broad definition on genetic tests could sweep in many tests for which current regulatory oversight is substantial and adequate. Developing new regulations based on such a broad sweep would be a step in the wrong direction.

For instance, because virtually all diseases have some genetic component but not necessarily an inherited component, if the definition is overly broad, routine tests such as cholesterol, glucose measurements, basic blood counts, DNA-based tests for non-heritable abnormalities would be included. These are well understood and accepted tests. They have markedly different implications and concerns from those that would apply in a discussion of heritable predictive tests. Sweeping them into any new regulations for genetic tests will unnecessarily complicate the delivery of these well-understood laboratory services.

The record indicates that laboratory tests are accurate, reliable and provide information relevant to the patients and their health care provider. ACLA reiterates that it's important to ensure that any proposed regulatory changes focus on legitimate risk specifically related to genetic testing. We pledge to work with this committee, the regulatory agencies and the health care community to identify those concerns and the regulatory approaches that will address those concerns without stifling innovation or negatively affecting patient access and care.

Thank you very much. Appreciate it.

DR. TUCKSON: That was good. That was great. It was responsive and specific and I think you get to making sense here as a good collaborator and an organization we need to hear from.

I think the question, I guess, ultimately will be is I hear your call and I would think that just assuming the sense of the committee is that we would not want to do things that are unnecessarily burdensome, regulatory for their own sake, bureaucratic or a pain in the neck just to have regulation so I think we would probably be in agreement there.

I think you heard the earlier discussion today about some of the things that the committee is legitimately concerned about for this and so I think what I'm just sort of hopeful is that off line in the days to come we would have your informed participation in helping us to solve our problem. I would assume that you're not as an association taking the position that nothing needs to be done further, just don't do dumb things.

MR. MONGILLO: I hope it came across loud and clear that the latter is what we're taking a position on. We also—I think we've heard the word "gap" a lot this morning and I've seen it in print and other places.

DR. TUCKSON: Right.

MR. MONGILLO: We're sort of leaning towards—it may not be a gap. It may be a small crevice that needs some little patching but I think there's room for negotiation and discussion.

DR. TUCKSON: First of all, I just wanted to get clear that you all were coming at this from a positive good—

MR. MONGILLO: Yes, absolutely.

DR. TUCKSON: --collegial way and not folding your arms and saying, "Heck no, over our dead body."

MR. MONGILLO: We certainly want to work with you.

DR. TUCKSON: Is there any specific question on this? I think this is very good. Does anybody have any questions?

Well, listen, for the record then you are available and I think we will be in consultation with you about what we do and getting your input because I think you have a lot to offer. Thank you very much.

MR. MONGILLO: Thank you very much.

DR. TUCKSON: Very well done.

Next we have Carol—

DR. RAUCH: Rauch.

DR. TUCKSON: That's what I said.

(Laughter.)

Wow! It's like a ventriloquist thing.

(Laughter.)

Hey, Carol Rauch. I believe you may be with the College of American Pathologists.

DR. RAUCH: I am. More importantly, I'm with Fay so I get instant popularity.

(Laughter.)

Everyone has been saying "hi" this afternoon.

Good afternoon. My name is Dr. Carol Ann Rauch and I'm Medical Director of Microbiology and Chief of Clinical Pathology at Bay State Medical Center. That's in Springfield, Massachusetts.

I'm here today on behalf of the College of American Pathologists and I want to follow up on written testimony that had been previously provided to this committee surrounding your discussion on gene patents in March of this year.

The college appreciates the opportunity to appear before you today to provide our perspectives on DNA based patents and licensing practice and their effect on access to quality laboratory tests.

The College of American Pathologists is a national medical specialty society representing more than 16,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories here and abroad. College members have extensive expertise in providing and directing laboratory services and serve as inspectors in laboratory accreditation programs.

The college has been a leader in developing quality improvement programs for laboratories, including programs related to molecular pathology and cytogenetics.

We are in the midst of a scientific revolution in genetics that promises extraordinary advances in clinical medicine. As medical specialists in the diagnosis of disease, college members recognize that genetic testing is an area of growth and change for pathology and medical practice in the decades to come. Pathologists, therefore, have a keen interest in ensuring that gene patents do not restrict the ability of physicians to provide quality diagnostic services to the patients they serve. Gene patents pose a serious threat to medical advancement, medical education and patient care.

When patents are granted, subsequent exclusive license agreements, excessive fees and other restrictive licensing conditions prevent physicians and laboratories from providing genetic based clinical testing services. As a consequence, patient access to care is limited, quality of patient care is jeopardized, clinical observations as the basis for new discoveries are compromised and training of health care providers is restrictive.

Throughout history, medical discoveries have progressed from the discovery of basic anatomy and histology and cytology, none of which are patented, to the more recent discovery of genes. The recent trend of using patents to monopolize gene-based testing services is a radical departure from historical precedent in clinical laboratories and it works against the goal of making these procedures widely accessible and affordable for the public. Especially troubling is the fact that under patent protection, the increasing understanding of the utility of the test, as well as the underlying disease process, also becomes proprietary, thereby imposing a profound change in how the profession and the public acquire knowledge about these rapidly evolving tests and the clinical utility in diagnosis of disease.

Physicians and scientists can easily and rapidly translate fundamental information derived from mapping the human genome into diagnostic genetic tests and use them for patient care. Because information about gene sequences is so fundamental to understanding specific diseases, patent holders can essentially gain ownership of diseases. Exclusive or restrictive license agreements on gene-based tests have been used to prevent physicians and clinical laboratories from performing genetic tests as diagnostic medical procedures and ultimately patients suffer because these services are less readily and affordably accessible.

Medical education and research related to laboratory testing are also threatened. In fact, college members have received cease and desist notification letters from patent holders or exclusive licensees indicating that continuing their patient testing would be patent infringement. Examples of diseases where testing has been halted due to patent enforcement include breast cancer, Alzheimer's disease, canavan disease and Charcot Marie tooth.

The college, like SACGHS, was awaiting completion of a study by the National Academy of Sciences Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation and subsequent recommendations and provided testimony to this NAS committee.

The study recommended that policy makers take appropriate steps to prevent the increasingly complex web of intellectual property protections from impeding potential breakthroughs in genomics and proteomics research and the access for the public to those findings. Specifically, it recommends that congress consider legislation to exempt research on certain aspects of patented technologies or inventions from patent infringement liability with a goal of promoting scientific discovery. The report also recommends that owners of the patented technology of certain gene based diagnostic tests should establish procedures to allow others to validate these clinical test results. If these patent holders do not take these steps voluntarily, the report suggests that congress consider in the interest of public health whether work to validate such results should be shielded from liability. This single clinically focused recommendation falls short of recommending specific protections for physicians and other providers of clinical laboratory services against gene patent infringement enforcement.

The college has supported policy recommendations and advocated for legislation in congress that would extend protections to laboratory physicians. Information provided to the NAS warrants the need to provide protection for the medical use of genetic information, including that derived from laboratory testing. The NAS report clearly outlines concerns regarding the negative impact of gene patents on medical practice. However, it did not provide recommendations to address the data gathered. We, the college, therefore, ask the SACGHS to carefully review the information in the NAS report on the clinical impact of gene patents, consider further investigation of this impact and develop recommendations for the Secretary of HHS to address the growing negative impact of gene patents on clinical testing in the United States.

In summary, we are facing the unprecedented situation in which a single patent owner can prevent physicians throughout the country from performing diagnostic procedures that use certain gene-based tests. This sets an extraordinary and dangerous precedent for patients and actually all of medicine and strays from the constitutional and social purpose of the patent system to promote progress.

Therefore, the college believes that current practices in patenting and licensing of genetic

sequences must be reexamined to ensure that gene-based diagnostic tests are widely available and affordable for the greatest public benefit.

Thank you for your attention to these matters.

DR. TUCKSON: Well, thank you. Let me just say that we are—as hopefully you'll have a chance at least to either stay or hear about the discussions tomorrow because we really are in agreement that we need to look at very carefully that gap between the NAS report and clinical issues.

DR. RAUCH: That one is bigger than a crevice.

(Laughter.)

More than spackle.

DR. TUCKSON: All right. I particularly appreciate having the American College of Pathology weighing in on this and what I really hope is that you, through your presence here, are signaling that the college's resources and its intellectual experience is available to this committee.

DR. RAUCH: Absolutely.

DR. TUCKSON: As we work through this. I think that one of the things that we have identified as a committee as being exceedingly important is having the role of physicians in these issues more substantive and more involved in the process. Quite frankly, we don't get enough of it and so I just want to make a special note, and if you would take it back to the college, that we appreciated your taking the time to be here and that we hope that you'll keep those lines of communication open as we try to work with this in the subcommittee level going forward.

Are there any other questions?

One of the things that we are comforted by is that Dr. Leonard is very much involved in your work and that's helpful.

MR. DANNENFELSER: Well, I just wondered maybe while she's here if I could ask, we had a discussion earlier about co-development with the private sector and the public sector, and to the extent that there is significant government dollars involved in the development of certain products, what can be done in terms of limiting patent protection in that case that might not already be done? I don't know if you could address that.

DR. RAUCH: Put in a quarter and you'll get a long answer.

MR. DANNENFELSER: Maybe you could get back to us.

DR. RAUCH: With all due respect, I think I would monopolize quite a bit of time addressing that but I would like to commit our full support on behalf of the CAP and know it's one thing to identify the problem and another entirely to work out the optimal solution that meets everyone's needs.

DR. TUCKSON: Well, if there's a way that you can—again, I think that you—as we work with you, if you could be prepared for helping us with that.

I guess the other thing would be just as you go back to your colleagues at the college, your message is very clear about what you don't want. I think what would be helpful to us again is if you were to put yourself in our situation and sort of look at some of the testimony or some of the discussions that we've had to sort of say here are the concerns that we have to work through.

By the way, we have your written comments, I'm sure, available to the committee.

DR. RAUCH: Yes.

DR. TUCKSON: The real issue now is to go beyond that to, okay, here is how to address the issues that we have to grapple with at the level of granularity.

DR. RAUCH: Right.

DR. TUCKSON: You put a marker down but now the question is how do we work through it and we would really, really appreciate that kind of guidance as we go forward.

I know we're close to needing to move on. Did somebody else have their hand up? Did I miss somebody?

See this is again Joe Telfair tries to get me to recognize people that aren't there.

Thank you very much.

DR. RAUCH: Thank you.

(Laughter.)

DR. TUCKSON: That goes without saying.

(Laughter.)

Michele Schoonmaker?

DR. SCHOONMAKER: Schoonmaker.

(Laughter.)

DR. TUCKSON: I started out going down hill.

I do know you're with the Association of Molecular Pathology.

DR. SCHOONMAKER: Yes. Thank you. Good afternoon. My name is Michele Schoonmaker and I'm here today as a member of the Professional Relations Committee of the Association for Molecular Pathology, that's AMP.

AMP is an international medical professional association representing over 1,400 physicians, doctoral scientists and medical technologists who perform genetic testing as well as other testing based on knowledge derived from molecular biology, genetics and genomics.

AMP members practice their specialty in academic medical centers, community hospitals, independent clinical laboratories and federal and state health facilities.

On behalf of our membership, the Executive Council and the Professional Relations Committee of AMP has reviewed the SACGHS document entitled "Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment and Disease." We would like to take this opportunity to applaud the committee's efforts in such an important undertaking.

AMP supports the concept for this project. We anticipate debate about many of the issues identified in the committee's report but are hopeful that the information derived from a large population study will facilitate clinical applications. We believe that the policy and process issues identified must be thoughtfully and actively pursued. We will provide detailed written comments before July 31st, which will include our concerns regarding scientific and technical issues of the project. However, today we would like to focus our comments on two facets of this report of great concern to our membership, clinical validations of research findings and patient safety.

As molecular pathology laboratory professionals, our members will undoubtedly serve as the interface between the public and scientists in any such endeavor. Consequently, policy decisions regarding the study that touch on the HIPAA privacy rule and CLIA are of great concern to us. While the draft report states that an investigator has no therapeutic relationship with the subject, there is no doubt that our members do have a relationship with their patients with all the attendant clinical, legal and ethical responsibility.

AMP members direct CLIA certified laboratories that would be appropriate locations for clinical validations of research results prior to reporting to subjects. The members of AMP are prepared to engage in substantive discussions to define the clinically relevant information which should be returned to the individual subjects and in what manner.

In addition, we also recognize our obligation to pursue the best interests of our patients. We note that the draft report focuses heavily on the scientific aspects of this project but our experience as clinicians and scientists leaves no doubt that the clinical importance and applicability could be immediate. Recognizing the very significant role our members will play in this effort, AMP strongly recommends that the processes and policies relevant to clinical implication and, importantly, patient safety must be specifically addressed now rather than later.

AMP appreciates the opportunity to address the committee on this very important endeavor. We reiterate our commitment to participate not only in pursuing the success of this project but in translating the results of this effort for the betterment of public health and patient well-being.

We invite you to contact Dr. Wayne Grody, the chair of the AMP Professional Relations Committee, if we can provide additional information. Thank you.

DR. TUCKSON: And, just for the record, you said that we're going to get some—a more-another set of more detailed comments by July 31st?

DR. SCHOONMAKER: 31st, correct. Yes.

DR. TUCKSON: Terrific. Thank you very much by the way.

Hold up. I've got to look around the table first before you go. All right. Thank you so much. I appreciate it. Thanks for taking the time.

Well, I know I won't get the last person wrong because I actually know Judy Lewis and I actually can say her name.

DR. : We had planned that just with you in mind.

(Laughter.)

DR. TUCKSON: Judy, International Society of Nurses in Genetics.

DR. LEWIS: Yes, sir.

DR. TUCKSON: I got it right.

DR. LEWIS: Very good. My name is Judith Lewis. I'm a professor of nursing at Virginia Commonwealth University in Richmond, Virginia. However, today I'm here to present testimony on behalf of the International Society of Nurses in Genetics, which is an international nursing specialty organization dedicated to fostering the scientific and professional growth of nurses in human genetics. We are pleased to submit comments to the committee regarding your document, the draft report on policy issues associated with undertaking a large population cohort project.

ISONG supports the document's intent to support preliminary and intermediate questions, steps and strategies in the five areas identified. The policy areas identified in the draft are appropriately focused and the issues are organized in appropriate categories and addressed in such a way as to give policy makers sufficient understanding of the importance of considering a large population cohort project on genes, environment and disease.

ISONG believes it's essential to involve and engage the general public and the nursing community before moving forward on such a complex and expensive endeavor and we'd like to make the following recommendations that will strengthen and clarify the document.

The first one won't surprise you at all, Reed, which is to broaden health care providers, to providers and patient care personnel, including nurses, social workers and psychologists, and other health care professionals;

To reword the following statement regarding the public's engagement to make it strong and that statement is "the public's willingness to participate in a large population project will be assessed before embarking on such an expensive endeavor." It is essential that the public be engaged before the initiation of such a project. Additional measures to assess the public's interest and willingness should include focus groups with representative community-based agencies, including lay health care workers.

Since nurses are present throughout the health care system and provide care, education and management to individuals, families and communities, it is essential to seek engagement and input from nurses and nursing organizations, especially around recruitment, approaching, educating, informed consent, privacy and confidentiality, and enrolling various subpopulations. Nursing associations such as the American Nurses Association, the National Black Nurses Association, the National Hispanic Nursing Association and others must be approached.

Please include nurses in ongoing consultation with the international community and the private sector to explore opportunities for collaboration.

Please specify nurses and nurse researchers as important members of a multi-disciplinary team approach for such a project.

And, finally, please include nurses in an independent standing committee for the duration of the

project.

Thank you.

And, just as an aside, it's very, very heartwarming as a member of the original Secretary's Advisory Committee on Genetic Testing to recognize that our work didn't fall into a great black hole but that some of it is actually being resurrected and used again. It has been very satisfying to sit there and it has been hard to keep my mouth shut.

DR. TUCKSON: By the way, it's not falling into a black hole. It's falling into a crevice, the dimensions of which we are unsure.

(Laughter.)

DR. LEWIS: Thank you.

DR. TUCKSON: That was really terrific. Thank you, Judy.

Any issues here? I'm sure we've got the written comments. I think the key thing is you make the point—oh, good, I'm sorry. Agnes?

MS. MASNY: Thank you very much, Judy. I just also wanted to draw to the committee's attention sort of supporting Judy's statement about the involvement of nurses. Steve mentioned earlier about sort of doing a systems approach and I think the nursing community really has taken this to heart as making a systems approach. With the efforts of HRSA and NHGRI nurses, a major endeavor was made to actually implement competencies for nurses across the board and, to date, from what I understand there is over 40 professional nursing organizations that have endorsed the competencies for genetics in nursing care looking at how genetics will impact all of patient care. So, I think, yes, nurses should be involved at all levels.

DR. LEWIS: That's true, Agnes, and thank you for mentioning that. The other thing is that if you look at the surveys that are done around public trust, nurses are out there and only in 2001 were we second to firefighters in terms of the profession that is most trusted by the general population. So if you're looking to gather engagement and have people who the public see as trustworthy, it's the 2.8 million nurses who can help you the most.

DR. TUCKSON: Judy, thanks an awful lot. Really appreciate you taking the time and we'll definitely be obviously following up, and I know you won't let us not follow up.

DR. LEWIS: Absolutely, you know I'm watching you, Reed.

(Laughter.)

DR. TUCKSON: As we turn it back to Emily, here's our challenge: We have got to resolve the unfinished amendment discussion from right before lunch. We need a consensus statement so that we can agree on that one so we need somebody as Emily—she may actually propose it but I'm giving you a chance in the next ten seconds to figure out the consensus statement. Then we've got to march through the rest in an orderly and quick and efficient way by 4:00 o'clock because we're going to switch topics. So the committee is going to have to be on its best behavior now and really drive through to things that get us to consensus.

Emily?

**FULL COMMITTEE DISCUSSION (Continued)**

DR. LEONARD: Can I ask a procedural question as well while you're getting your slides up on the screen, which is the existing draft recommendations we have not seen in this form, have we?

DR. WINN-DEEN: The existing ones, yes.

DR. LEONARD: These existing ones we've already seen?

DR. WINN-DEEN: Yes, they were discussed in March.

DR. LEOANRD: No, but that's the yellow version. Did we finalize these because I'm looking at these and going I haven't seen them in this version.

DR. WINN-DEEN: I don't know what staff has done.

DR. LEONARD: Will we have a chance to review and ask questions about these?

DR. WINN-DEEN: Yes.

DR. LEONARD: Okay.

DR. TUCKSON: So let me just hold down on this for just a minute because let's not rush pell-mell at the moment until we know what road we're running down. We're going to run rapidly down a road. I just want to make sure I know which road it is.

At the end of the day the process, Emily, I think is what people want to know about.

(Simultaneous discussion.)

We're having a consultation here.

DR. WINN-DEEN: Debra seems to think we have. So do you want to just suggest?

DR. : Yes.

DR. WINN-DEEN: Between the yellow sheet and the white sheet that the wording is different.

DR. : Yes.

DR. WINN-DEEN: Is it just order or is it wording?

DR. : There's wording also.

DR. WINN-DEEN: What editing did you—can you just comment on what editing, if any, you think you did?

DR. : 14 on the yellow and 12 on this.

MS. GOODWIN: I think some of them just got moved around.

DR. TUCKSON: All right. Regardless—

DR. WINN-DEEN: So we lost two?

DR. TUCKSON: Okay. All right. At the end of the day—

(Simultaneous discussion.)

DR. TUCKSON: Let me not have a meeting inside of a meeting so let's worry about it in a minute.

DR. : Yes.

DR. TUCKSON: Okay. I don't want to do two meetings at once. Look, let's just be clear. The expectation of this discussion, Emily, for the full committee is once we have reviewed all of these recommendations, what will you do with this information and when does the committee—what are the—once they approve something here or we get these consensus statements, what happens with it? Does it become locked into law? Does it come back to us again?

DR. WINN-DEEN: Our intention is to try and get input so if people have comments they still want to make on the substance of the recommendations then we're going to have a working group task force meeting in September, which will be a wordsmithing meeting by the task force, a smaller subset of this group. And that wordsmith set of recommendations will then come back to the full committee in November for final approval. We elected to learn from our experience with coverage and reimbursement and not try and do wordsmithing at the full committee level. So our main concern is to make sure that we have captured everybody's thoughts, concerns and then it will come back to the smaller group for really working through.

DR. TUCKSON: So let's just make sure. The assumption is we're giving the committee—we're giving our subcommittee the opportunity to hear our guidance, our ideas, we're working through the big policy issues and we're coming to consensus on the broad scope of each individual recommendation. They will then take that and now work it with real language and with he said, she said and ands and buts, and that will be fine. You can influence that process outside of the meeting if you would like by sending information in to them but at the end of the day you'll get another document back that you will review and approve. So there's multiple stages in this.

DR. WINN-DEEN: Right. And it will come to you in sufficient time to read and digest it prior to the November meeting. It will not just appear in your table folder.

DR. TUCKSON: All right. Let's march through.

DR. WINN-DEEN: Okay. So we were discussing the issue of human subject protections and rationalization of OHRP Common Rule versus FDA. There were a couple potential recommendations here. The first was to encourage FDA and OHRP to work together to enhance the consistency of their human subjects research policies. We heard this morning from Mike that it's not just OHRP. There is as many as 17 agencies that follow the Common Rule. That extends the scope, if you would, of how many agencies would have to work together to come to some rationalization. We could still recommend that they attempt to do that.

The other option is to ask the Secretary to work directly with congress to create a new human subjects protection that would basically replace both the FDA and the Common Rule with a new "harmonized recommendation."

So I'd like to just hear sort of brief comments. I don't want to rehash the issues but I'd like to hear comments from the task force on those possibilities.

Sylvia and then Andrea?

MS. AU: I am just a little confused. What Mike and Steve have said today is do we really need this as a recommendation to the Secretary since it addresses—I mean it's something that is broader than from genetics and it seems like if you're a researcher and you need to address both the FDA and the Common Rule that you better be a smart enough researcher to address them to be able to use it for both purposes.

DR. WINN-DEEN: Okay. That is legitimate.

DR. FERREIRA-GONZALEZ: I wanted to make a similar comment. One of the issues of point here is that the definition of human subjects. The FDA uses a little bit more restrictive definition of human subjects but recently the FDA has put in a draft guidance on use of anonymized specimens in a retrospective way where now you can get waiver informed consent. So maybe the recommendation of this committee could be that instead of looking at revamping all the regulation is ask the FDA to look at these draft guidance and maybe put in a proposed rule making to change some of the way the FDA is looking at these specimens.

DR. WINN-DEEN: Steve, can you comment?

DR. GUTMAN: Yes. I actually think that's a pretty reasonable suggestion. Before I'd go to congress, I'd see if we couldn't cleverly—I actually believe if you change the reg so it doesn't make this—link the sample inextricably to the subject-- what Mark Sobol calls sacrilization of a sample—I actually think you could work around this with an easier fix than congress. If that turned out to be wrong, I guess you could always go back to congress but that's not—

DR. WINN-DEEN: Right. So have you had any IRB feedback on the de-identified sample or anonymous?

DR. GUTMAN: Generally very positive feedback. It produces a lot more room for exploratory studies in the way that we had imagined and again, specifically, for this particular area, I actually believe the informed consent you're going to need for the drug development is easily—with some wordsmithing could be fixed to cover the diagnostic part. So I actually think you might be trying to fix something we're already trying to fix and the recommendation might be just to encourage FDA to do it.

DR. WINN-DEEN: Is there any way to have the agencies craft some kind of informed—or at least maybe make some short guidance on what are the issues from each of the two different approaches and how one might create a human subjects protection for your study that would meet both requirements?

DR. CAROME: Well, from our perspective--I suppose you're talking about samples that have been anonymized to where all identifiers have been permanently removed or the samples have been coded in a way in which the researcher receiving the coded specimens—there are prohibitions against them never receiving the key to the code. We've essentially declared in a guidance document a year-and-a-half ago that that's not covered by our regulations because it doesn't involve human subjects. So we stepped back and removed ourselves from that and so it's the issue of to what degree do the FDA regulations

apply and they've tried to do some carving out. I think to the extent that this is limited to FDA moving that forward as far as I can under current statute that's where this should probably best go.

DR. WINN-DEEN: Okay. Yes, Sarah?

MS. CARR: Steve, you indicated before that this is an enforcement action, the guidance, and that you're going to have to put it into a proposed rule. Can you talk about—say a little bit more about what the time frame is for that and whether the committee might—if it decides to support this approach that would recommendation from the committee in support of that next step be helpful or might that be the tone it took?

DR. GUTMAN: Yes. Well, again, it certainly can't be harmful so it would be neutral. I think it probably would be helpful and, of course, I'm just too old to continue to predict time courses for any work product but we will take this seriously. It's really—if there has been a single issue that I've dealt with that actually is actually counter to the Critical Path it's actually making it harder to get samples.

DR. WINN-DEEN: Okay. Sarah?

MS. CARR: One more thing is that I think it might be helpful to understand the extent to which, if at all, there's any difference between your guidance and the coded specimen guidance of OHRP and its interpretation. Is that—does your guidance bring—is it the same, in effect, as the OHRP? So maybe there is no—

DR. GUTMAN: Well, but that would be worth exploring so a recommendation to explore that as we move towards that because I actually think that they're very close. I don't think that they're probably quite identical. I think that we were not as generous as we could have been and that that's a reasonable recommendation also.

DR. WINN-DEEN: Okay. So I'm going to refer it back to the staff and task force to try and craft some words and they may be calling both of you to just try and double check to see if what they craft is an appropriate representation of this discussion.

All right. So let's move on.

(Slide.)

We had discussed previously the issue of returning research results and had a draft recommendation on how to manage this when there's clinical decisions that could be affected. I think we heard testimony just a little bit ago about how this will be dealt with in the realm of when you're doing large population studies, at what point are you going to really want to return results. So I think this is an ongoing issue. I'm not sure we have anything more to say unless some of the new people have something they'd like to say on just the subject of asking HHS to provide guidance to researchers on how and when they might be able to return relevant results without violating CLIA.

DR. EVANS: Again, the only thing I just want to bring up is this seems like a subject that is far broader than just pharmacogenomics.

DR. WINN-DEEN: Right. I agree.

DR. EVANS: Yes.

DR. WINN-DEEN: Okay. All right.

(Slide.)

The next one was failed drugs. Again we heard from Janet Woodcock this morning about the really abysmal success rate of drugs entering Phase I and coming out the other end of the Phase I, Phase II, Phase III. This is actually with choosing the target and the clinical development program which has yet another quite substantial funnel effect. The question is could some of these drugs make it through the gauntlet if, indeed, there was a test that identified the subset of people who would benefit from them.

(Slide.)

So the staff put together a potential—this was an area we had not made a recommendation on as a task force and so this is a new potential recommendation on potentially asking HHS to promote public access to the data on pharmaceutical products that have failed to demonstrate effectiveness in studies

involving a general population cohort but might be candidates for a more tailored approach.

I had some pretty substantial comments so I'm going to take the chair's prerogative and just give you my comments on this in terms of just the logistic feasibility of doing something like this.

So in scenario one the clinical trial didn't collect the appropriate samples so there's no sample to screen. The clinical trial was not designed to collect biologic samples and so there's nothing there to go back to so that's sort of a nonstarter.

If a pharma company did connect the trial with sample collection but didn't screen for markers so they hold the samples and they hold the results of the clinical trial, I'm not sure what the mechanism is to allow public access to HHS or any other means to that dataset. That dataset belongs to the pharma company and they can choose to do what they want to do with it. If they want to see that drug pop out the other end, they can do a biomarker analysis and see if that would help but that's their commercial decision to make. Again this is not a public dataset. It's not an HHS issue.

So it seems to me that the only time that this might potentially be applicable is if there was a cooperative group kind of study that was done under NCI or NIH funding where there were biomarkers or samples taken and drugs tested but again most of those cooperative group studies are on drugs that have at least obtained FDA approval. It's not part of the FDA approval process.

So I'm really not quite sure, and maybe if people have some suggestions, how we could have HHS involved in a publicly accessible database when the data from a drug trial typically is not public data. That's my quandary of sort of the basic issue here. So I'd like to hear comments and feedback if we should just say that this really is not an HHS issue but pharma companies certainly could make use of this approach.

Steven?

DR. TEUTSCH: I am not directly connected to a lot of the senior level for a pharma company but, as I think most of you realize, there's now a clintrials database, which has been the subject of a lot of discussion but the trials are now at least posted on clintrials.gov so that the nature of those trials are made available and it seems to me that the process would be for those that are interested in looking at those that have failed compared to the—you can probably get the results of some of those trials because there's a commitment to get some of that information out that the ones that have "failed" or even the ones that are successful that it would be up to diagnostic and other companies that have ideas as to how they could be optimized to get back in touch with the sponsors and develop the kind of collaborative relationships that we talked about earlier with the public-private or private-private kind of discussions about the additional studies that might be conducted. So I'd probably tie it to something that already exists rather than developing an entirely separate process.

And earlier your—I think there's going to be great reluctance to share that information in any kind of a public forum in a very early stage because those are considered proprietary data.

DR. WINN-DEEN: Right. That's my concern.

Francis and then Agnes?

DR. COLLINS: So, Emily, I think you're quite right that the reality factor here is not going to be consistent with the idea that pharmas are going to open their books to a failed trial and show their competitors what they have done or not done. If they possess the biospecimens and have a reasonable hypothesis of how they could stratify their participants in a way that gave them the chance to get drug approval, who in the world is going to be more motivated than they are to do that? So it doesn't seem to me—if you're trying to stimulate action here—that this would necessarily need a stimulus if the specimens are there and the hypothesis is there.

I would take just one point, though, to say that NIH does conduct Phase I, II and III trials, especially for rare diseases. It's not purely a pharmaceutical industry activity. But in those circumstances, again it's a little hard for me to see why you would need some sort of special inspiration for sunshine to be directed on that process because anybody conducting a clinical trial is going to be

highly motivated to try to figure out whether the drug did something good for somebody. And in the current era if the specimens are there and if there's a reasonable idea about what genetic variance might have correlated with response, I think the people running the trial are going to jump all over that so this one does seem a little anomalous.

DR. WINN-DEEN: Agnes?

MS. MASNY: I am sort of in agreement as well and that maybe our first option that we had, the first recommendation, looking at fostering the collaborative opportunities and the co-development of pharmacogenetic products, that maybe just—you have—maybe you could list one of the opportunities under there as failed drug products in that initial recommendation rather than making a whole new recommendation here.

DR. WINN-DEEN: Okay. Michael, did you have something?

Any other comments? Okay. So I think we will take that out as a recommendation and maybe just mention that rescue of failed drugs is part of that whole companion diagnostic scenario as one of the motivations for using that rescuing of drugs that otherwise would have failed.

(Slide.)

Okay. So the next issue for which we did not have a recommendation and we're looking on whether there is some whole committee input into what we could have here basically is in a scenario where there might be an existing drug and a new indication for that that would be governed by pharmacogenetic tests.

So, again, I don't know if this is something that we need to have as a separate line item but it was brought up as a potential area that was a gap in the previous set of recommendations.

So right now there's not a lot of financial incentives to identify subpopulations that could benefit from dosage adjustments or, well, there's a fairly high—there's an incentive for high risk of adverse drug reactions, particularly if there's a chance your drug would be taken off the market. But for the other part if the drug is widely approved there's not a lot of incentive to add a PGX test if it made it through without it.

So any comments, requests? Francis?

DR. COLLINS: So I'm a little unclear just in terms of the language that's in the document here. I think we're under point F. Am I right? It sounds as if there this is talking about new indications for existing drugs whereas I thought what you were describing was primarily using pharmacogenomics to do a better job of adjusting dose as opposed to a totally new indication. This would be the expected indication but a means of trying to personalize and optimize the dose.

DR. WINN-DEEN: Right. Yes. So I'm not really—

DR. COLLINS: Which is it?

DR. WINN-DEEN: Either/or, I guess. The question is can we imagine a scenario where someone would need to be tested in to use a new intended use?

DR. LEONARD: Yu can do off label uses of drugs that are approved. I mean physicians do that all the time.

DR. WINN-DEEN: Right.

DR. COLLINS: I don't think this—I'm just trying to think of a scenario in which again this would be specifically applicable to pharmacogenomics and I'm kind of coming up empty.

DR. WINN-DEEN: Okay.

DR. COLLINS: To me there isn't a lot of—

DR. WINN-DEEN: All right. That's brainstorm consensus.

DR. COLLINS: But before you throw it away, the way you were verbalizing this a minute ago, though, I think is a circumstance where you're in the post-marketing phase. I mean we talked about warfarin this morning where a drug has been around a long time. It isn't necessarily ideal in terms of the incidence of side effects and you've got a chance to try to do better by trying to use pharmacogenomics to

improve dose adjustments. It does seem to me there is a research priority for drugs that have been around a while that we haven't fully capitalized on and I would have thought that this committee would want to endorse the importance of that kind of activity which probably won't be supported in the pharmaceutical industry because if you have a drug that's already approved you're not going to be terribly motivated to try to narrow its scope or add an additional complication to the labeling that might scare away some prescribers. So this may very well turn out to be our job for NIH and other federal funders.

DR. WINN-DEEN: Yes. I thought we had addressed that particular issue in one of our other—

DR. COLLINS: Well, if so, that's fine.

DR. WINN-DEEN: --recommendations here. We have so many recommendations now it's hard to remember what they all are. Okay.

So your recommendation is that we just confine ourselves to potentially looking at the application of PGX to existing drugs and if the utility of existing drugs in the broadest sense could be improved.

DR. COLLINS: Right.

DR. : That's number five.

DR. WINN-DEEN: Yes. I thought we already had that as a recommendation.

DR. EVANS: I mean that's a pretty central feature--

DR. WINN-DEEN: Yes.

DR. EVANS: --to everything we're saying. I think the confusion arises because of this issue of new innovations.

DR. COLLINS: Okay. Back in the earlier one.

DR. EVANS: I don't think that is really what anybody was—

DR. FERREIRA-GONZALEZ: How about G? You're talking about post market surveillance.

DR. WINN-DEEN: Yes.

DR. COLLINS: That's really adverse drug reactions as opposed to dose adjustment although they're connected.

DR. LEONARD: 5A is recommending these—to encourage rigorous prospective randomized studies to test whether promising pharmacogenetics findings actually translate into improved patient care, which is what warfarin is all about.

DR. COLLINS: Right.

DR. EVANS: We could add something on there about for new drugs and for established drugs, right?

DR. WINN-DEEN: Yes.

DR. EVANS: I mean to make that clear.

DR. WINN-DEEN: Okay. All right. So in the interest of moving forward here, we'll just pass that opportunity by to make a recommendation. I think that was fairly clear input from the team.

(Slide.)

This was an area of intended use population. I think this gets back to what we were just talking about that we would like to see all of the trials using a genetically diverse set of patients doing the trials and should it be apparent that there is some potential subset to try and work towards understanding what the actual genetic basis for response is versus saying that one racial subset appears to respond better than others.

So I think this was trying to get at the issue of--the way Bayh-Dole ended up getting approved is that we really—we still don't really understand the genetics of what's going on there and we're using race basically as a surrogate marker for whatever the actual underlying genetic marker is. So that's just a recap of recommendation three.

(Slide.)

For the next issue, which was Phase IV clinical trials for PGX, the question arises that in a normal Phase III trial for use of a companion diagnostic you probably still have a relatively small subset of

people being tested and if you're trying to use your pharmacogenetic test to avoid, say, adverse reactions you really want to follow that out into a Phase IV to verify that that actually is working as hoped.

So the question arose, and maybe FDA can clarify this a little bit, as to what FDA can actually do. There's a requirement sometimes for Phase IV studies but there's also—it has been widely reported that Phase IV studies don't seem to happen as agreed to and I don't personally understand the mechanism for either requiring Phase IV studies or what obligation that pharma companies have to conduct them, what enforcement FDA has if they don't conduct them. Is there just some education that we could get on that subject?

DR. GUTMAN: Allen, you're going to have to field this because I actually don't know what the authorities for Phase IV studies are.

DR. RUDMAN: I'm not quite sure what the questions are actually.

DR. WINN-DEEN: Well, so my specific question is if you could explain to the committee how a Phase IV study comes to be requested by FDA and what mechanisms there are available at FDA to assure that one that's requested actually gets designed and executed.

DR. RUDMAN: A very interesting question and it's a very appropriate timing. Phase IV commitments—when you have enough information to approve a drug but you have certain questions that you really want to follow up on to optimize the dose or for other reasons like safety or whatever reason there is. These are sometimes very limited, sometimes not at all and sometimes quite extensive.

I'm not going to get into the question of when or why a company should be doing this or the timing on it. I think that's a whole different issue for the moment.

In terms of—what I would say is the companies do sign off to do this at the time. It's part of the agreement for the approval and so they are committed to doing it.

I'm not quite sure if particularly for the older applications if the timing was really ever specified. I think that's part of the issues involved.

DR. WINN-DEEN: Okay. So is that changing now that when they—if a company was to be approved tomorrow and part of that approval was that they agreed to do a Phase IV study, is there agree to do it with—to have it designed and begun within a certain period of time and completed and reported by a certain period of time?

DR. RUDMAN: My understanding is that the FDA is now looking into improving the process and really looking into doing it in a systematic manner rather than doing it ad hoc case-by-case. So they are trying to really improve the entire process.

DR. WINN-DEEN: Okay. I guess what I'm trying to get to is are there some tools that FDA would like to see in their tool belt to help them get that done that we could make a recommendation on in terms of assuring that Phase IV studies, once agreed to, are actually executed or is that something that you think FDA has under control?

DR. RUDMAN: Well, they are actually starting it now and I think that's what's going to come out very shortly. For me to say right now I think would be to preempt the process the FDA is trying to go through right now to really improve it systematically.

In terms of the issues you have up there, identifying genetically based subpopulations as a condition for enrollment, that's true. Actually this goes to the question of trial design, whether you're going to be looking at enrichment designs or adoptive designs--

DR. WINN-DEEN: Yes. So let me flip—

DR. RUDMAN: --or other designs.

DR. WINN-DEEN: --to the recommendations.

(Slide.)

So maybe this is—should all new drugs that require a companion diagnostic be subjected to Phase IV study? I think that's a question. I'm not sure that we should take that out of the hands of the experts at FDA who are actually looking at the data but that was a potential recommendation.

The other question is in terms of keeping track of adverse events. Is the database and the reporting structure sufficient to allow that to really be properly tracked in the absence of a Phase IV study but just out in general use?

DR. RUDMAN: In terms of option one, I don't know if you really want to mandate Phase IV clinical trials. In cases where—you know, safety and efficacy has been shown to be in all commerce. Do you really want to require them to do another study when you've already shown that a product works in all commerce? I mean the way it's going to say "mandated" seems to implying that you are using the word "required." Okay. So I'm not sure if that's really what you meant.

In certain cases certainly it might be beneficial but I think that has to be worked out.

In terms of option two, I'm probably not the right person. Probably Dr. Seligman, who has just received—he's in a new position currently but he's in charge of safety, Office of Drug Safety. And my understanding from his talks was that actually we have both passive and what you might call active methods for looking at adverse reactions, including databases from a number of different organizations, where they look at the—they go out there and actually search their data as against waiting for the data to come in.

So, I mean, that's my knowledge of it but I think Dr. Seligman would be the best person to talk about those in detail.

DR. WINN-DEEN: Okay. Any comments from the task force? I mean, I personally agree that I don't think mandate is the right word in option number one. Maybe they should consider that for each drug at least with a companion diagnostic whether there's actually enough dataset to not want to do a Phase IV but I'm not sure it's up to us to mandate things to FDA.

Steve, I'll let you respond to that and then Francis had a comment.

DR. GUTMAN: Yes. I mean, you are emphasizing here the drug side which seems to me to be appropriate. Of course, the device side also has the capacity. It's not called the Phase IV study but it's a condition of approval study. So we actually have some tools for follow up on our side. The good news is that there's—perhaps because of the Vioxx fallout—there's renewed interest within devices at doing a better job at post market studies and surveillance so I think we're taking this much more seriously.

The bad news is we don't have a rich culture certainly in the diagnostic area to draw from so we're sort of chartering new ground here but the news that sort of trumps it, and actually HER2 is the case in point, is that you can't stop people from studying and observing the behavior of the—at least on the diagnostics. The pathologists are very intrepid beasts and they are still arguing—actually still arguing about IHC versus FISH versus proficiency tests. So I actually think the pathologists will worry about this for you on the diagnostics side.

(Laughter.)

Our—we do have efforts to look at—again on the diagnostic side—look at the passive reporting system. They are about to try and convert it to an electronic medical device reporting system. The good news is that will make it easier to use, friendlier, easier to sort through the data. The bad news is garbage in/garbage out and that that won't guarantee we're getting high quality data so that's still something to work to attain.

We're also fooling around with a new system, part of MEDSON, called LAVNET in which we are also trying to on a very pilot basis explore active surveillance as opposed to passive surveillance. Certainly this is an exotic, sexy enough product area that if we could identify the right partners these would be the kinds of products we'd be interested in following. We're not really interested in hemoglobin or glucose or sodium in quite the way we used to be. Not to suggest that they aren't important.

DR. WINN-DEEN: Right.

Francis, you had a comment?

DR. COLLINS: Yes, but this is more about option two.

I think the goal of option two and of AERS, in general, is to try to identify those rare instances where an already approved drug is causing side effects but not at a high enough frequency that it was necessarily picked up in the Phase III trials. This is an area that I think is of great interest to the public and to the FDA and we've had quite a lot of discussions between FDA and NIH over the last year about ways that this might be facilitated, both in terms of a reporting system but from a perspective of trying to not only figure out what happened but why it happened. How could you not only have a reporting system but something that is linked into obtaining a biospecimen on the individual who has suffered an adverse reaction so you could begin to try to assess what the reasons for that might be. Now we have such mechanisms as doing whole genome association studies and it becomes possible to actually do that even with modest—hundreds or so—numbers of cases you might have sufficient power to do that.

So I guess the AERS system as pointed out here does not necessarily have the search-ability that you'd like to have in some ways because of the lack of a controlled vocabulary but it also doesn't provide you in many instances with a link that gets you actually back to the individual and gets you a biospecimen, and that seems to me maybe that ought to also be highlighted here. If you're going to have a really effective system it ought to have all of those pieces so it becomes a real engine for research discovery and then for implementation of what you've learned as far as better public health.

DR. WINN-DEEN: Sure. Okay. That's a good comment.

Steven?

DR. TEUTSCH: Just a couple of points. One is I didn't see anything in here that is particular to pharmacogenomics that we've made the case as to why this is any different than any other kind of drug issue in which case we need to have general things. I think Dr. Collins made a good point that the AERS system is pretty good for rare events that are unusual that are easy to find but it's terrible for finding common things like myocardial infarctions that are not likely to even be reported within this kind of a system and that's the reason for developing the entire other set of safety related studies, whether it's surveillance studies that are more systematic, registries or other kinds of things to find those kinds of things, which I suspect are at least as great interest as these rare events but that's true for any kind of drug discovery process.

I think we'd have to make a case as to why we think things—what are the things that are different for pharmacogenomics that would warrant this or else we just indicate that this should be done in a general sense.

DR. WINN-DEEN: Well, I think the question probably comes back to what Francis said about getting this biospecimen. Ultimately if we could understand—if we could identify those who had these events, it might potentially be possible to get a specimen from them and do the research so that you could find whatever the biomarker is, whether it's a genetic marker or protein marker, expression marker, whatever, so that a companion diagnostic to weed those people out could potentially be developed. I think that's sort of the link to pharmacogenetics in this—

DR. EVANS: We ought to say that. That's what we ought to say.

DR. WINN-DEEN: Yes. I mean, in my mind that's really what it's for. It's not just to find adverse events. So what? The whole point is to get—

DR. EVANS: Apply pharma—we should encourage ways of applying pharmacogenomics to figuring out these adverse reactions.

DR. WINN-DEEN: Okay.

DR. TUCKSON: I think, Steve—I see that we have another committee member's hand, I just want to make sure—I think, Steve, what you both, and James, are trying to get at here is that the preamble to all of this in terms of about how we get to why there is a recommendation, why is it—what is it about pharmacogenomics that makes this particular topic especially important or especially relevant? I think we do need to be real clear that we—that we are not solving—that we're solving a problem that has somehow or another been identified as being important. I think that that's really what you're getting at and I think

what we're sort of doing is we've got the cart behind the horse right now because we're jumping into the recommendations.

So the question to make sure of is either that your question is making sure that we are, in fact, responding to why this or your question is have we made—have we convinced you that there's a problem that has to be solved?

DR. TEUTSCH: Right. I mean, I think the point I heard here was that you should use pharmacogenomics as part of solving problems that are detected with any kind of adverse event system. I mean that you can make a recommendation about. That's a unique application of pharmacogenomics to understand safety issues as opposed to anything unique about pharmacogenomics that makes them have specific safety issues because there are plenty of small studies out there that are just like these that will be for limited populations where it would be applicable.

DR. WINN-DEEN: Right. So, unfortunately, we've got sort of processing where we have sort of the contextual report being presented to you separately from the recommendations. Our hope is that when the thing comes together that what you'll have is you'll have in the report here's the problem, here's the issue, and then here are some recommendations that address that issue.

So we'll make sure that this part here about adverse events really is listed in that section where—I think everybody would agree that there's drugs that have been pulled off the market because of adverse events that were probably quite beneficial to a large number of people but aren't available to anyone now because a small number of people had bad stuff. So there's—I think there is some incentive on both sides to try and figure it out to report the events, to get specimens and get the research done to really figure out what's going on.

DR. TUCKSON: I'm not sure, though, that—by the way, I appreciate that. I was trying to listen to it carefully. Did we decide, though, is it because—is this issue on the table because of the concern about bad things or the opportunity that this provides from a technical point of view to have benefits across all of health care? I think that's really what Steve is getting at and I'm not sure which of his two questions is what we're—is the problem we're solving. Is this a problem we're solving or an opportunity that is available for this field to contribute across the board, and I'm not sure which one this is.

DR. WINN-DEEN: Well, I mean, personally I think if you're going to talk about adverse events, the horse is out of the barn. The drug is released and presumably it has been released without some kind of a test. Otherwise you wouldn't have released it. So you need to have Phase IV studies to find—or Phase IV or some kind of registries or monitoring to find adverse events and then you need to have a system to see if there's a rescue strategy possible to identify those people who are at highest risk from taking a specific drug.

Did you want to say something? I'm sorry.

DR. RUDMAN: I'd just like to point out there are actually two sides of this. One is certainly the adverse events side of it to minimize adverse events but the other side is the efficacy side. It is actually that both equally—not equally important but they both have a significant contribution. There was the brief discussion this morning about Iressa and the possibility of using Iressa where you have increased efficacy in subpopulations.

The other side of it is, of course, the safety issue. This really addresses the safety part of it but you might want to think about addressing the efficacy side of it.

DR. WINN-DEEN: Right.

Gurvaneet?

DR. RANDHAWA: That was actually my point, also. I think one of the issues is the drug may be approved on the efficacy side on surrogate markers and not on health outcomes which may actually be different once it goes in the real world. I'm not sure that it's only FDA's concern. I mean the other health agencies, whether CMS or AHRQ, are equally interested in finding out what the health outcomes are of drugs. So I would suggest broadening the recommendation to look at not only the safety but also

the benefit side and making it beyond just FDA but other relevant HHS agencies who may be interested.

DR. WINN-DEEN: Okay. I think we're going to have to do some more work on that one and put it in the right context.

DR. TUCKSON: One of the things you might want to consider as we go forward is—just as we look at the available time—is how much energy to put on the options and how much energy to put on the actual topic area.

DR. WINN-DEEN: Right.

DR. TUCKSON: So you might, as you guide us through that, making sure that we do have consensus on the G's and the H's and the so forth.

DR. WINN-DEEN: Right. So we're moving along here.

DR. TUCKSON: Thanks.

DR. WINN-DEEN: Okay. So we're going to sort of switch gears here on to some of the issues that were raised on direct to consumer marketing of pharmacogenetic tests.

(Slide.)

In some ways pharmacogenetics is a simpler case than an inherited genetic disease but the question is still whether a consumer is equipped to receive pharmacogenetic data and act on it in the absence of a health care provider partner. So that's really just framing the issue.

So there's four potential recommendations here. I'll just go over them briefly and then we can discuss the subject.

(Slide.)

I think it really boils down to at what point is the consumer informed enough to work with the information.

So the first option is that FDA should require the labels of the pharmacogenetic tests that are offered directly to consumers to include information sufficient to enable them to make their own informed decision on the use of the product and actually interpret their results.

The second option is that FDA should require as a condition for pre-market approval that companies offering PGX tests directly to consumers without the involvement of a health professional should make available telephone mediated genetic counseling.

(Slide.)

The third option is that you could move things to a level that's a CLIA waived test that's approved for sale over the counter and at the point where something is approved for sale over the counter then you're definitely marketing directly to consumers even if what's available over the counter is just say the sample collection device that's then sent into some central laboratory for processing.

And that anything that isn't approved basically for over the counter use would have to involve consultation with a health professional.

And the fourth option is, just due to the complexity of this whole area, the Secretary could encourage congress to pass legislation prohibiting the marketing of PGX tests directly to consumers without the involvement of a health care provider.

I just want to say that this is sort of the spectrum. It was not intended that we pick all of these but that we use that as sort of a discussion range for what we really want to say on where we think direct to consumer marketing of pharmacogenetic testing is today. There certainly are people that say you should know your CYP2D6 genotype and talk to your health care provider about it any time you have a drug prescribed to you. That's sort of one school of thought.

And the other is that this is really something that the physician should be managing and not the consumers.

So I just want to maybe have ten minutes of discussion on this and then try and come to some conclusion of where in this range of options we'd like to say something if we decide we want to say something at all about it.

DR. TUCKSON: By the way, as you contemplate this and make your decisions on this, do remember that we have got our direct to consumer activities outside of this and so one of the things you want to make sure you keep well in mind is the synergy between things that we're doing, and so as you make perhaps policy here that will be one thing where you have another process of informing this decision through our discussion around the FDA and other oversight on DTC so just keep that in mind.

DR. WINN-DEEN: Okay. Kevin?

DR. FITZGERALD: Yes. I just wanted to—looking at the first two, as we mentioned before, if there are difficulties with labeling and having the physicians gather the appropriate information from the labels, I'm not sure we should dump that on the consumer directly. So option one doesn't seem to be terribly viable in that regard.

Then the second one—I guess we probably run into the difficulty that we had before when we were talking about genetic counseling and the idea that if the company was going to make available this telephone mediated genetic counseling, what criteria would there be to say that these people are adequate to the task of doing the genetic counseling? Can you do single disease genetic counseling? Do they have to be masters level? Can there be nurse—we went all through this before.

DR. WINN-DEEN: Right.

DR. FITZGERALD: So rather than get into that swamp again, I'm tending more towards the other side of your options there.

DR. WINN-DEEN: Okay. Yes?

DR. EVANS: I'm just trying to think about who would be using this and in what context and whether it's worth thinking about. I don't think people are going to be using this for decisions about the dosing of their Sudafed when they have a cold. Right? So you've already got—you have physicians integrated into the process already in the sense that for most of the things we're talking about a prescription is required. Right? So who is—it's going to have to go through a physician, don't you think? Is that fair?

DR. WINN-DEEN: I personally hope so but that's just my personal opinion.

DR. EVANS: No, I'm just—well, practical standpoints—

DR. WINN-DEEN: Right. No, you're right.

DR. EVANS: --aren't the physicians going to implicate into this?

DR. WINN-DEEN: Joseph?

DR. TELFAIR: I had a comment on that but you already made it.

DR. LEONARD: Well, one of the concerns I have is not only does the physician write the prescription but then your health insurance only will provide coverage for the amount that the physician has written you for so you can only take the dose that your physician gives. You can't go self-dosing. But on the other hand I've heard reports of people who have had adverse reactions because of a physician not taking into account the pharmacogenetic variability of that patient and they go get their CYP2D6 or whatever done and take it to their physician and their dose gets adjusted and they feel much better. It's a New York Times article that I use sometimes when I'm talking about pharmacogenetics.

So I'm not sure since physicians are not integrating pharmacogenetics into clinical practice that we want to take away the right of patients to at least have access to this if they need it.

DR. EVANS: Right, and patients—

DR. LEONARD: Or could benefit from it.

DR. EVANS: And patients bring things to us all the time and say, "What about this? What about that?" And that's part of practicing medicine.

DR. LEONARD: But maybe what we do want to do is—I mean as Reed was pointing out, maybe we want to encourage the FDA and FTC to take a specific critical look at the marketing and use and safety of pharmacogenetic tests in this FDA-FTC collaboration that we initiated or encouraged them to do. Maybe that would be the right framework in which to put this and then the FDA and FTC have

expertise in doing this and could look at the pharmacogenomics that's being marketed direct to consumers.

DR. WINN-DEEN: So let me ask you how you guys feel about option number three. So if a test—this is a completely hypothetical but if a test was to pass the requirements to be marketed over the counter to a consumer with all the requirements for sixth grade language readability and a clinical trial that shows that people can understand the directions and properly interpret the results that come back, is that a scenario that we would feel comfortable? Is there any scenario we would feel comfortable--I guess, is really the question—in direct to consumer marketing? Not just any genetic testing. Not here I do want to specifically limit it to pharmacogenetics which we had identified, SACGT, as sort of the lowest risk genetic testing environment. Is there any scenario in which we would feel that that might be okay?

DR. LEONARD: Jim is right because nobody is going to be able to do anything with it because the physician is the only one who can write the prescription.

MS. AU: I think for the most part genetics is so complicated that most public—they don't really understand it. To allow them to choose how their genetics could affect their drug or how the drug will affect by the kind of gene that they have. A lot of them, they just don't understand it.

DR. EVANS: I don't understand how my car works either.

DR. WINN-DEEN: Right.

DR. EVANS: And I don't have to get permission to buy one. I mean—

(Laughter.)

I don't know. I think that since there already is a mechanism in place—people aren't writing their own prescriptions and aren't saying I think I'll start taking warfarin and dose it with GX, I think that—three isn't too bad it seems to me because there are circumstances. People should be able to—if somebody really wants to find out whether they are a CYP2D9 metabolizer or fast metabolizer or not, it's okay. I don't think that's threatening or toxic information to them so I don't think we should be too proscriptive.

DR. WINN-DEEN: Barbara?

MS. C. CHEN: A lot of time people get information that will over alarm them that might not be that great anyway.

DR. WINN-DEEN: Well, of course, it would depend on if you got something through in an over the counter scenario that all of that stuff would have had to have been addressed as part of going through—there's quite a rigorous approval process to get anything approved for over the counter use and there's a relatively small number of tests but I can tell you that people who are taking home pregnancy tests might be alarmed by the results. They might be happy and they might not be happy.

(Laughter.)

But we don't tell them they can't take the test.

(Laughter.)

DR. EVANS: It just seems to me that unless we can identify and see a real risk to people—I mean that's—we obviously need to step in and make recommendations if there are risks to people but I'm having trouble figuring out where there would be a big risk to people and then getting their genotype.

DR. WINN-DEEN: Okay.

DR. EVANS: But I'm open.

DR. WINN-DEEN: I'm going to let Barbara say something because she has been very quiet today and then we've got Andrea and Gurvaneet.

DR. McGRATH: I think I'm just mimicking what we're saying. I think that we can decide in this room that it's good or not good to have direct to consumer advertising but it's out there. It's not going to end. It's going to just increase, I think. So you can't make a recommendation to say there should be no direct to consumer advertising because it's out there and people take prescription drugs, whether or not they're prescribed for them, so those are the realities. So I think it makes more sense to

sort of make some—maybe some of the ideas that Debra Leonard suggested and make some recommendations about drugs in general and educational materials but I think it would be kind of silly for this committee to say there should be none where I think there's no question that it's going to happen.

DR. WINN-DEEN: Okay.

DR. TUCKSON: Thank you. I want to suggest given that we've got time on the agenda for DTC tomorrow and it's on the agenda formally, maybe we might just—I think you've given us a good sense of it. Let's revisit this when we get there. I'm real worried about the fact that we've got 45 minutes left and we've got to get through a bunch of other ones.

DR. WINN-DEEN: We're actually doing okay here.

DR. TUCKSON: I'm glad you're confident.

(Laughter.)

I'm the one that gets blamed if we don't bring the train in on time. She's gambling with my money here.

(Laughter.)

DR. WINN-DEEN: Okay.

DR. TUCKSON: By the way, if we do finish before the allotted time, we'll come back and talk some more about DTC.

DR. WINN-DEEN: Okay. Well, I'm going to skip over it.

(Slide.)

This is prioritization of pharmacogenetics research needs. Obviously in any society there's a finite funding pool so the question is how do you prioritize what areas would be most useful to go after? One potential straw man recommendation was that HHS should convene a group of experts to develop criteria for prioritizing pharmacogenetics research needs according to feasibility, public health need and impact on public health. The group should also assess both current and potential PGX projects and rank them according to their relative priority.

So my first impression on this, again taking the chair's prerogative to make a comment, is that this sounds a lot like an NIH study section or the process that NIH would go through to identify before it put out a request for proposals the areas that would be most beneficial. So I'm not sure we need to convene a new group of experts.

I don't know, maybe, Francis, you can comment on how NIH comes to decisions on funding.

I don't know if Rochelle is still here.

DR. COLLINS: Yes. I was also looking around the room because it would be really helpful to hear about our pharmacogenetics and genomics efforts that are underway at NIH, which are organized particularly through NIGMS with Rochelle as the major leader. So this involves many institutes. There's a pharmacogenomics research network that you may know about that has been in existence for several years. There's a database.

DR. WINN-DEEN: Is there coordination with the other AHRQ and all of those groups that might be interested in outcomes research?

DR. COLLINS: Yes, although I can't tell you the details and I'm sorry Rochelle is not here to answer that question.

DR. WINN-DEEN: Okay. So I think as a recommendation that it's good to have a group of people who are well informed to create a prioritization list. I don't have any problems with the basic concept of this recommendation. I just didn't want it to appear that we were making a recommendation when there's already activities ongoing within HHS. So maybe we need to just do our homework a little better on exactly what's going on.

DR. COLLINS: Yes, given that at least in this meeting we haven't heard a report on what's already underway in this regard from someone like Rochelle, it seems a little premature to endorse a recommendation of this sort which implies more is needed.

DR. TUCKSON: And maybe as we follow up on this from her, let's also try to be clear about to what purpose this prioritization—I'm not sure I know what it is we—again, what do you do once you—is it—prioritization for what purpose is not—

DR. WINN-DEEN: Well, I think that the concept was to examine sort of from the public health benefit point of view, if government money is to be spent on something, how does that decision making process come into being. Should you do esoteric disease X or should you do warfarin?

DR. TUCKSON: No, but the key thing was that—

DR. WINN-DEEN: So I mean there's some—

DR. TUCKSON: --I think the operative issue was, again given the relevance of this committee, if government money were to be used—

DR. WINN-DEEN: Right. Specifically HHS money.

DR. TUCKSON: --then what would be the priorities. Is that basically what this—okay.

DR. WINN-DEEN: But I guess my question is do we need to make a recommendation that we should—HHS should convene a group of experts or is such a group of experts already convened? If we think it's already convened then this is sort of redundant. If we think that there are some issues and it needs to be more broad based specifically across agencies then maybe this is a worthwhile recommendation.

DR. COLLINS: So I think there—

DR. TUCKSON: Isn't it—

(Laughter.)

DR. WINN-DEEN: Well, it depends upon if we approve going with the large population study or not.

DR. COLLINS: I think it's fair to say there is good coordination between FDA and CDC and NIH. What I'm less sure about is some of the other HHS agencies but again I guess because setting up groups of this sort involves a fair amount of energy and time commitment on the part of the people who have to set it up and who have to participate in it, it would be nice to be sure that this is not something that this group would already agree is covered and I think it may be.

DR. TUCKSON: So we will get the input.

DR. COLLINS: Yes.

DR. WINN-DEEN: Okay.

DR. TUCKSON: Good.

DR. WINN-DEEN: Okay. See, Reed, we're just moving right along here.

(Slide.)

So this recommendation really was trying to look at the more complex side of drug metabolism and looking at more than just a one gene at a time, either systems biology or looking at multigenic issues. We know that there's a lot of what—dietary influences on metabolism. There's drug-drug interactions that can affect drug metabolism.

(Slide.)

So the question was whether we wanted to sort of move to promoting a wider thinking process in the research into understanding drug metabolism with a goal being that if you understand it in a more holistic way you can have even better predictor tests available and so I think warfarin is a good example.

We've heard there's two genes but they contribute not everything to how you get to an effective dose and there still are other biological factors that have to be taken into account. How do we make those pieces come together so that you can have the most effective treatment for patients?

So I don't know where we are with trying to think more broadly in terms of the grants that are being funded and starting to really understand that it's not a one gene kind of a thing in a lot of cases where we're going to have to deal with more complex—not just more complex genetics but also understanding all the other sides of things. There's this big environmental study that's going on as well.

I don't know how much influence that might have.

So I think this was really intended to just outline pretty clearly that it's a complicated area and as we move forward the answers may be also more complicated and the need for—it may not be a test but a panel of tests or whatever that give you what you really need.

Francis?

DR. COLLINS: A couple of comments. I mean one is that this is not just about drug metabolism. This is also about variations in the target for drugs and all of the other things that are involved in the pathway.

DR. WINN-DEEN: Right.

DR. COLLINS: So maybe that ought to be broadened a little bit. Again this is really, what you're describing here, very much a central goal of this collaborative enterprise, a very significant one for NIH. The Pharmacogenomics Research Network, the PGRN, which is associated with this database, Pharm-GKB, that attempts to try to collect a lot of this information about pathways and how variations in particular genes and proteins may play a role in differential drug responsiveness. So I don't think it would be fair to imply that somehow this is not already considered a very high priority. It's hard stuff. I mean anything that gets into the realm of systems biology is hard stuff and that's sort of what you're talking about here is marrying pharmacogenetics with systems biology.

DR. WINN-DEEN: Right. So I guess we could come down on just saying that, that it's hard stuff and that this is going to take some devoted time and effort to really study properly with the recommendation being to make that time and effort to do so or we can just throw up our hands and say way too complicated, let's save that for somewhere down the road and tackle the things that are more straight forward today. So again just trying to get some sense from the committee of the spectrum of opinions on where we are and what things we can practically recommend at this point.

DR. RANDHAWA: I will be happy to give one part of the spectrum of opinion here. Both in this recommendation and the previous one there is sort of an assumption here that understanding more about genes is going to play a larger role in improving health outcomes of a given disease. Warfarin is a great example. I've been hearing a lot about it in this meeting and it's an appropriate example. But one can say, okay, we can understand all we can about genetics and understand precisely what dosage to give starting out therapy but how does that factor into some therapy that's going to be given for five years, ten years? How many weeks the patient may decide not to take the drug, how about dietary factors that may influence the role of the dosage of warfarin or other medications that may influence bleeding level that has nothing to do with genetics?

So in terms of research funding, should we be thinking about ways we can improve compliance and adherence to the warfarin where if you make an impact of 20 to 30 percent of patients who are compliant to maybe 30 percent of patients being compliant, they will have a maximum benefit of both as opposed to understanding what about genetics at the front end of dosing. So I think it's a good discussion to have.

In terms of prioritization, we perhaps need to think about different approaches to improve disease outcomes and not just to focus on genetics and how genes may improve the outcomes.

DR. WINN-DEEN: Okay. Other comments?

Can we get in touch with Rochelle if she's the right person to just give us a little synopsis on where we stand in terms of the more complex approach here? I mean if you think staff can just get in touch with her and do that or whatever is the right chain of command.

DR. COLLINS: If we could track her down and try to get her back here before 4:00 o'clock, would that be useful?

DR. WINN-DEEN: Potentially.

DR. COLLINS: We'll try.

DR. WINN-DEEN: Okay. Francis, maybe if you can even just get her on the phone. She

doesn't have to physically get back here. Okay.

(Slide.)

So the next area that—we're just going to keep going on here because we're going to try and make as much progress as we have or we can--really concerns the issue of neglected diseases or orphan diseases. So I guess sort of two separate things. One is neglected diseases that affect large numbers of people but they don't happen to reside in the countries that have a lot of money to address them so they don't get a lot of attention because the health care dollars in those countries are spent on more fundamental things like food and water supply and maybe, if you're lucky, vaccination.

So the question is, is there a role that we should be thinking about or is pharmacogenetics just so far off the spectrum there that in limited health care dollars it's never really going to be applied?

And the other end of the spectrum is for rare diseases that are in developed countries but they're just so infrequent that they don't have—again this is a commercial incentive issue. There's not enough people with the disease to develop the research that really is needed to ascertain if a pharmacogenetic approach might be helpful. There's a gap between the number of individuals who qualify for orphan drug status versus orphan diagnostic status. So we just—I wanted to just sort of frame those two issues and then we can go through where we are with that.

Comments, Kevin?

DR. FITZGERALD: Yes. I was just wondering—I'm not sure that it's all encompassed by saying a system for fostering for neglected disease because I was just wondering—I mean you can have the same disease and still have neglected populations of people—

DR. WINN-DEEN: Sure.

DR. FITZGERALD: --who share that disease. I thought since our emphasis here is of public dollars for public health, maybe we should add that in there somewhere to say or neglected diseases or it's not so much like saying, geez, I'm neglecting this disease. It's the populations that are being neglected. It's the people that are being neglected. I don't really want to foster the disease but I think that would put the focus back more on the public health question because here in Washington, D.C., we can talk about the neglected populations that share perhaps the same disease that other people do and the question is can this technology give us another way of addressing that situation rather than saying this is going to solve this disease and say is this going to help us address this particular public health issue.

DR. WINN-DEEN: Okay. Joseph?

DR. TELFAIR: Okay. Two things. One is—and they're both sort of in this—sort of spills out of the same recommendation. This issue is addressed pretty well by some organizations already. For example, the American Public Health Association has some clear policies along the lines of what Kevin was mentioning in terms of the issue of drugs for populations themselves that are neglected or under served, and there's a lot already that exists there and it's very easy to get.

The other thing along the same lines is that Dr. Alexander, as you know, with rare diseases and I think that it may be worthwhile to get an informed opinion about that part of it—of what's—because there's a lot of discussion already and there's a lot of discussion that has been had, and there's actually, from my understanding from presentations by him because of the committee that I serve on, is that there is some work already in that direction. I'm not quite sure. I don't know if Dr. Collins knows or not and whether they've had interactions with Dr. Alexander in rare diseases or not but I know that there has been some discussion. I think it would be really helpful to this group—this committee before something is decided to find out what's really going on there, and I think it would be very informative to do. So I'm just recommending for this particular set of options to actually have a conversation with those two groups and the staff can do that because the policies by APHA are pretty straight forward and I'm sure when Ms. Terry talks to you tomorrow she can fill you in as well about what's going on there with genetic alliance and also there is contacts and I can give you names a little bit later for APHA. But also with Dr. Alexander, I think, having him, himself, or someone from his office talk—either come and talk or have a

conversation about can give you some informed decision. If there's a committee that's going to have a meeting on this already then maybe the committee itself can meet them because they're just right here. I know that he come to every one of the other meetings that I go to and I've heard this conversation so I'm just bringing that up.

DR. WINN-DEEN: Okay. Thank you.

Debra, did you have something?

DR. LEONARD: This recommendation seems kind of like mom and apple pie. I feel a little uncomfortable making a recommendation about how NIH should pay attention to populations of diseases that maybe neglected either the population or the disease. When you really want to get kind of the best bang for your buck, if you will, and if cardiovascular disease is a leading killer of Americans or spent cost of health care dollars, then I don't know that we necessarily want to be recommending that they not spend money there and spend money on rarer diseases. So I'm not quite sure—while I agree that it would be nice to take care of absolutely everybody and every disease, also my concern is with neglected diseases. Is there the basic research of appropriate therapies, et cetera, being done so that pharmacogenomics would even have an impact at this point or where are we in the treatment of those diseases?

So I just feel quite uncomfortable with this recommendation.

DR. WINN-DEEN: Did you want to say something?

DR. TELFAIR: I just want to say I think both of those questions could be addressed by the organizations that you have. I mean, I guess the way I see this is part of the work of the group is to advocate also for those that we can but I think it should be a very—advocacy needs to be in a real sense realistic. So there are these policies where they are realistic and they take into account a lot of these other issues, and I think it will be—before the group even decides to run or not run with this—to really listen to what those other things are saying and I am addressing this to try to—I'm adding on to what you have said but I do think that would be real helpful.

DR. WINN-DEEN: Right. So maybe, Suzanne, we could get in contact with these folks and maybe have them join the task force meeting for a short period in September just to sort of take a little bit of that task force time to understand what's going on already.

DR. TUCKSON: Just as we do that, again I want to—I think just we want to keep in mind again the committee—the need for—as we get to the end of this process here, a sense of prioritization, a sense of what are the things that we can do as a committee and what things you can't do. And I think that one of the things I appreciate in Emily's comment—the same thing we did on the coverage and reimbursement report—and for those that are new to the committee, I would urge you to take a good look at the front piece of that report. We sort of basically put our work in the context of a health care delivery system that is already stressed and extraordinary with 45 million uninsured people, da, da, da. So at the end of the day there is, as Emily, I think, appropriately has introduced into this conversation, a sense of reality. I think we also had a moment ago a discussion about the NIH committee that may or may not be working—the HHS committee that may or may not be working in terms of coordination. That gives you a sense, also, of prioritization.

So as you think about all these recommendations, which we are going through appropriately now—we're doing the hard slogging through the mud of each of these recommendations, at the end of the day we have to really keep in mind we've got to come back and sort organize these, prioritize these, which are the ones that make sense. Of course, you can't get to that elegant conclusion until you punch each of these out and see what's there and turn the rock over and see what it means and that kind of thing. So I just want to just keep that context in mind.

We're not going to do everything. You can't do everything. You've got to focus in on what makes sense so we have to keep drilling through this process.

DR. WINN-DEEN: So we have a half an hour in our discussion time.

(Slide.)

We have a number of things to cover. Measurement of health outcomes was an area where we already had a draft recommendation and we discussed it at the previous meeting.

Gurvaneet, did you have anything else you wanted to say on the health outcomes because I know you're quite interested in the outcomes area?

DR. RANDHAWA: Yes. I would again like to stress that not all the different kinds of study types and methodologies that we can use to gather real world data are in here so there is—so I'm looking at recommendation 5A and there's an emphasis on regular prospective randomized studies to test whether promising PGX findings actually translate into improved patient care.

It's not clear that that is really the best study design to get into translational research. And here when I say translational research, I mean post-marketing translation into clinical practice. And whether it's through pragmatic clinical trials or whether it's through information gained in registries or some sort of additional database or health plan database, it's not quite clear here as to what the advantages and limitations of these different data gathering activities are and how we can use all of them to get a better prospective of not only the benefits but also the harms and the patient safety.

DR. WINN-DEEN: Okay. So I think that's an area where we can maybe ask the Lewin Group as they make the next revision of the report to look at these sort of categories of outcomes research and how they might be done and at least set the stage in a little bit more functional detail.

Barbara, did you have something?

DR. McGRATH: I just want to jump in real quickly. I'm been chewing on this all morning. Dr. Woodcock said something really intriguing to me when she was talking about the early—early on trying to talk about the field of pharmacogenomics and how important it potentially will be and barriers to its discovery. She said something--unless I misunderstood her saying that randomized controlled trials will not be the only paradigm, that we need a paradigm shift. I thought that was a revolutionary statement. That's why I wasn't sure I heard it correctly.

DR. WINN-DEEN: Particularly for FDA.

DR. McGRATH: Well, yes. So I wondered if that really is true and we say that are we—is the bureaucracy ready to accept that. Would NIH and the FDA really accept evidence-based coming from something other than RCT and you bringing that up with outcome research reminded me of that again, though she was talking about it on the front end as well. So I guess I would just—I don't know if that's one of the recommendations that we think about because there's other recommendations in here about research process but I—it was an intriguing statement.

DR. TUCKSON: Just only a friendly amendment to your question is maybe not so much what NIH accepted. I think the operative group is would CMS accept it and would the private payer—purchasers of health care accept it. I think that's really where the issues are and it's a legitimate question and one that I think is worthy of further exploration.

DR. TEUTSCH: These are going to be really central issues for things particularly as we deal with rare events and small populations so it's unique to many of the things that we're dealing with and AHRQ has certainly taken the lead on many of these to try to develop better methodologies that will pass the rigor test that people will find acceptable.

I think one of the things that we could do is to talk about an effort to really solidify the method so that we do have some good alternatives to RCTs that are credible which have dealt with the major issues that are the threats to validity problem because most of these are observational and that can put all of this on a much firmer footing when we are not going to have RCTs or we're going to have to retrospectively go back through trials and deal with them. We need that kind of methodology. I think that's something we could ask to be developed.

DR. WINN-DEEN: Okay. Other comments?

DR. TUCKSON: I just want to make sure we don't lose something here. I think that what's important again as we come back to the prioritization and the definition of—I mean what is it that our

committee can do? I think, Steven and Barbara, that you're both sort of focusing in on this continuing challenge of genetic exceptionalism. What is it about the pharmacogenomics that's different than other things? What are either the opportunities or the challenges that it presents? Why are those issues important to the American people? Why are they important for this committee to decide that it's worthy of attention?

I think that I just want to keep all of our very smart committee members thinking about that question. How would you write that paragraph? I'm not asking you to do this at this moment but I think you have to really start to write that paragraph. How is—what is it that is so special about pharmacogenomics that it requires or provides the opportunity for different things that, therefore, require an investment in time and energy, whether it's Francis' point about calling for a committee takes time from busy people, that we would feel strongly enough about it to ask for that, or money because we think it ought to be specific new studies that need to be funded or new regulations that congress ought to pass.

I mean I think we have to be very—we're getting to the point where we have to be very disciplined about why it is that this is special and what is the opportunity that we have to make a difference in ways that are meaningful that need to be addressed that would not otherwise be addressed were we not to exist.

You should think about writing that paragraph. I think that will discipline your analysis of this a little bit.

DR. WINN-DEEN: Okay.

(Slide.)

I want to try and move ahead here. We have linkage and compatibility of clinical databases. I think this is an area where there is a lot of effort going on between the group that's focusing on this whole electronic medical records issue and trying to rationalize FDA databases and the clinical database that is part of your FDA submission.

I don't want to really dwell on this but if people have some specific comments, particularly the new folks, in terms of anything else that we should be concerned about to make databases that are in existence more useful and searchable so that basically if the knowledge is already there you can get to it. So that's really not about new knowledge as much as it is about really trying to pull together the knowledge that is existing somewhere in space today.

Sherrie?

DR. HARRIS: Actually I think my comment is more relevant to the previous recommendations. I didn't realize we were going to move off 5C. HHS should identify federally managed databases such as, et cetera, et cetera. I would just encourage the committee to think about other federal databases or federal opportunities. For instance, the Department of Veterans Affairs have electronic medical records on almost seven million veterans that might with collaboration between VA and HHS might provide considerable opportunities for health outcomes research.

DR. WINN-DEEN: Do you think it might be useful to just—as much as we sort of pull together all of the activities within HHS in terms of different things they are doing, to try and pull together in one place a list of databases and what they—sort of the basics of what they have or what their point of being is?

DR. HARRIS: You mean all of these different federal—

DR. WINN-DEEN: Yes. Just so you sit here and you say NHANES, HCUP, what do those really have in them and what exists today, and then we can at least have a sense of where there already is data. To task someone with trying to make databases compatible is, I know, quite a monumental thing to think about but would there be ways in which a controlled vocabulary, for example, within all HHS databases or all—

DR. HARRIS: Yes, I was actually thinking of something very different in encouraging collaboration to address the purpose of where you're going rather than looking at compatibility.

DR. WINN-DEEN: Okay. All right.

Joseph?

DR. TELFAIR: I just want to contribute. I agree with the recommendation but I just want to say that it already exists, what you just asked. MCHB, HHS, HRSA, MCHB has a blue book on outcome data and it already exists and it looks at pretty much all the databases in the HHS system, and some that are related, and then linkages and contacts and that sort of thing. It's a volume that already exists and I can give the reference to the staff.

DR. WINN-DEEN: Okay.

DR. TELFAIR: If they need it.

DR. WINN-DEEN: That would be really helpful, I think.

DR. TELFAIR: Sure.

DR. WINN-DEEN: I mean if it already exists we don't need to be worrying about it.

DR. TELFAIR: The part that doesn't exist is what Ms. Harris was recommending that kind of needs to be worked out but the other part of deciding what are the actual mechanics, it's done.

DR. WINN-DEEN: Okay. Can we not have side conversations, please?

I'm learning.

Okay.

(Slide.)

So then we had a recommendation on evidence base for economic value of pharmacogenetics. I think we all recognize that this is a really important part of showing that something will benefit the system and either reduce the cost of adverse events, reduce the cost of being on the wrong meds, reduce the cost of hospital stays while you're getting on to the right dose. If you're going to put a test in front of a drug, which has a cost to it, hopefully you're saving that cost in spades down on the other end. If not, you're just going to be increasing the barriers to access and the cost of delivering medicine.

(Slide.)

Again I think this is one that we've had in the book for a while and if there's other comments from any of the new folks, I'll just ask you to send those in to the staff.

(Slide.)

Government officials' knowledge of pharmacogenetics, this was one of the gaps that was identified as a place that maybe we should say something about that. I think it really is aimed at the people that are having to interact with decision making in terms of pharmacogenetic tests so either people who are involved in regulating a test getting on to the market, reviewing filings or the people who are regulating the payment for that test and how it would be integrated into clinical practice. They ought to have some basic understanding of what this is and so whether there's a way that all those kind of people that are involved throughout HHS and making decisions about pharmacogenetics can get a little primer on it so they have at least some basic set of knowledge that they're working from to make informed decisions rather than uninformed decisions. So that was really, I think, the source of this recommendation.

Reed obviously has a comment.

DR. TUCKSON: I would urge that this not be one that we would put a lot into. I think it's sort of pejorative and I mean this sort of basically says that the people that are doing—reviewing science and so forth and so on don't have mechanisms to keep up and they're not—without our prodding, they would be slipshod or uninformed or not doing continuing education. If that's the case they ought to be out of here.

(Laughter.)

DR. WINN-DEEN: Okay. Well, we'll just put that as the recommendation. Learn what you need to know or you're out of here.

(Laughter.)

Any other comments?

I think we've acknowledged that education about new fields is an important thing and so I think I'll differ from you a little bit in that we ought to encourage and make it possible for the people who need this knowledge to get the knowledge they need through some kind of continuing education mechanism. I think that was really the point of this to provide continuing education for those that need it.

Any other comments?

DR. FITZGERALD: We could probably solve that by just getting rid of insufficient understanding and just emphasize the education piece. As law makers have an insufficient understanding there. Just change it to law makers have a continual need of being updated on these issues or something like that would probably solve the pejorative aspect.

DR. WINN-DEEN: Okay.

Debra?

DR. LEONARD: Why are emphasizing "law makers" as opposed to everybody else who is going to learn about pharmacogenomics, too?

DR. WINN-DEEN: Well, I don't think we emphasize law makers without taking into account everybody else but—

DR. COLLINS: The recommendation sounds as if you're focusing this on HHS staff and I think I have to agree with Reed. The way it's currently phrased it's not just about the insufficient understanding in the preamble. The recommendation itself implies that HHS staff are generally unable to get themselves up to speed on any new topic unless somebody comes along and beats it into them and I'm not sure that would be well received by HHS staff.

DR. WINN-DEEN: Okay. That's definitely—okay.

DR. : Government workers.

(Laughter.)

DR. WINN-DEEN: You never know. My budget cut my continuing education this year.

DR. TUCKSON: Go to school.

(Laughter.)

DR. WINN-DEEN: Anyway—okay. I think I'm going to skip to liability issues because this is one that again we sort of danced around a little bit at the previous discussion.

(Slide.)

Whenever you have some recommendation that says you should do something this way, if you don't do something this way you chance—take the chance to be sued about it. So really the question was aimed at if there's a recommendation that a test should be used in conjunction with prescribing a drug, if you don't use that test, if the patient—there's several things. If the physician doesn't order it, is there a liability? If the patient refuses it and then has an adverse event because it was prescribed anyway, is there a liability?

So really we—not that any of us claim to be experts but we just thought that we should probably highlight that there—like any other medical procedure—there is some liability potential here and the question of when does something become "standard of care". Does it become standard of care when FDA approves a test and a drug? Does it become standard of care when more than half of the insurance companies pay for it or when there's a physician consensus statement that it should be used in a certain way? So we just wanted to highlight the potential for pharmacogenetic testing to create some liability issues and particularly I think the physician failing to order and the patient refusing to be tested are the two key areas that would be of concern.

Debra?

DR. LEONARD: What is also the liability of having genetic variability on a drug label but no dosing recommendations? So I mean there—we're struggling with this at New York Presbyterian hospital because we're trying to figure out how to use pharmacogenetics when there's genetic variability in the label. One of the things we're considering is what's our liability for not testing for this genetic

variability and yet there's not enough information out there to effectively us it clinically. So there's also this gray area of liability.

DR. WINN-DEEN: Right. So that goes back to when is something standard of care really. When you first discover it and you sort of know about it a little bit or when you've gotten to a clear—well, it's on the drug label but there's not a dosing recommendation. So then is it—so the question is should we try and—as part of this process—create a recommendation for either a group of experts to really establish what would potentially be used as legal precedent then or should we just discuss this in general terms and not really say much beyond that other than a study is required and the price of medicine is a difficult thing to regulate.

DR. LICINIO: I would like to say that I agree that the issue of dosage recommendation is crucial because it boils down to that in the end. I mean the test is useful to some degree but it basically has no practical utility unless you change the dose. If you're going to take the drug at the same dose there is—I mean you can be reassured by the test if you are a known metabolizer. But the point is really to address the dose and then the question is how do you address it and that's what's sorely needed.

So just saying that the dose needs should be addressed based on the results is not going to go anywhere. What is the doctor going to do, if anything? That's the crucial issue for the field right now.

DR. EVANS: I'm not sure what we're really doing with this recommendation in the sense that I don't think that the Secretary or our committee is going to be responsible for setting the standard of care. The standard of care is kind of a multifaceted thing and that applies whether we're talking about pharmacogenomics or whether we're talking about the best way to do a particular procedure.

So I am—I mean, I think this is a fine sentiment. I am not sure, however, that it's real productive to have—I mean, who would this committee—so this committee is supposed to explore these issues and devise strategies and recommendations but who would those go to and what power would they have. I just—I have trouble with—

DR. WINN-DEEN: Yes, so I guess—

DR. EVANS: --I mean I think we need to really focus on advice to the Secretary that is practical tangible advice that you should act on this and you should do this. But as far as kind of what Debra referred to as apple pie and mom stuff, I don't know. I mean I think we run the risk of diluting our recommendations by having too many things here that sound good but I'm just not sure they are practical.

DR. WINN-DEEN: Right. Well, like I said, these were just up—they were areas that we identified at the last meeting that we really hadn't addressed so wanted to try and address them to have some conversation. There is nothing wrong with saying that this is a hole we don't want to step in or that it's inappropriate for this team to really comment on.

DR. FERREIRA-GONZALEZ: It might be more appropriate maybe to have the recommendation to HHS to develop infrastructure to have greater communication when the clinical practice guidelines or dosing recommendations are given that they could give to the right professional organizations or members of the different societies.

DR. WINN-DEEN: Right. Well, I think that's in some of the other recommendations.

DR. FERREIRA-GONZALEZ: Yes. So that will go back to that one.

DR. TUCKSON: One of the other things that you might consider here is again which of these recommendations are things that will support the involvement of the medical societies in actually being able to write the guidelines and the standards of care. So that may mean something to do with again having the available evidence and answers to the kind of questions that they need to have answered and so forth. That may be the way to tie some of these things together.

DR. WINN-DEEN: Right. I guess I was just concerned a little bit of say FDA approval was the bar then that's definitely an HHS thing and one would have to think about that as part of doing an FDA approval that once that happens that that has certain repercussions and we really haven't dealt with the whole ethical dilemma and payment dilemma of what if there's a test that's a companion diagnostic that's

required but the patient refuses the test. Are they still eligible for the drug or not? And if they are still eligible then does that create a sort of shower of stuff that happens where everybody says I don't want to pay for that test so just skip the test and give me the drug.

DR. TUCKSON: We have got three minutes to do two more so you guys are going to have to really move quick.

DR. WINN-DEEN: Okay. So I just want to go over what the other two are and then again solicit your written—well, there's actually three in my little book here, four, five.

DR. TUCKSON: I will tell you what then—

DR. WINN-DEEN: Okay. So let me just say that these recommendations 9 through 13 in my slide set here are ones that we talked about before. It would be useful to have input from anyone who hasn't had a chance to give input on to these areas. So it's basically best practices, distribution of information, interpretation of results, Medicare coverage. It would be quite interesting to know what the process is for Medicare and CMS could make a decision on that. And ultimately we would like to just probably make a recommendation that when we have electronic medical records they have a mechanism for including genetic test information.

I think those are pretty straight forward.

What I did want to take the next five minutes on is if there's also anything that people have for comments back to the Lewin Group on the draft report that they have written, if there is other issues—

DR. TUCKSON: Let me try it this way because I think this is important. Let me just ask you a question back. What we have done, and the committee should be commended, and Emily, for not only organizing but leading us through a very wide ranging menu of possibilities for this topic. I think that what the committee has certainly benefited from, from this discussion, is that we are pretty well now sort of all sort of up to speed on the varieties of things and we've actually shared some consensus building around what we think are important and not important, and we've fleshed these out.

I think we all have the sense that there's more work to be done on these, more sense of prioritization, more grouping, more lumping, sort of more analysis of this, and that is very important but I don't think there's any way that we as a committee, as we learned from the coverage and reimbursement process, unless we just slog it out detail by detail and keep going over and over it, you just don't get to a shared understanding where you actually can vote on anything as complex as this a couple of meetings from now. So this is good.

Now, Emily, what you are saying is that we've got this draft report in yellow that has a lot of text to it. The question becomes how does the committee read this now given everything that you have sort of gone through—you've got a sense of learning more about what these things mean, what's important and not important, how do you go through this and then comment on it and to whom do you comment in the days to come, and then what happens with those comments and how does it go forward?

So the question, Suzanne, is how do your staff support—want to solicit the committee's input on the yellow pages?

MS. GOODWIN: First of all, just for clarification, the yellow document in here is a lit review and is not a draft report. That is what the Lewin Group is working on right now. They're taking the background and they're going to be reorganizing it and setting it up so whatever recommendations are in there, there is some background information. There is laying out of the issue or the gap that has been identified and helping to set up the recommendations so that's what they're working on right now.

What I think would be most useful—and Sandy can correct or add to it—what I think would be most useful is to get some input from the committee members and ex officios about are there any specific topics that are not currently in the lit review but that you think are important that should be added as background and somehow help set up some of the recommendations.

DR. TUCKSON: Okay. Well, then—all right. So that's one way to do this is again you're providing information on this literature review and what's in it and what's not in it.

The second mechanism here--and let me just sort of by way of doing this formally and with extraordinary appreciation thank Emily for her taking the lead on a complex task. I think you all know and we're going to say it with sadness tomorrow but that Emily transitions off the committee at the end of this meeting and that is with sadness.

Let me just stop right now and thank you, Emily, very much for what you did.

(Applause.)

Now, what this means is that James Evans is no point. I'm deliberately not looking at him because I'm making sure that he's not withdrawing--

(Laughter.)

--given how much work there is and how complex this assignment is as you've seen and how hard it is. It's good. But James has got the point and passing the baton to James.

Now there are some other people on this subcommittee I do believe. Do we know who they are?

MS. CARR: Well, we neglected to include the names of the other task force members in Emily's slide presentation so our apologies for that but Jim, of course, who is going to become the chair, and Julio is on—Julio—and Debra and Kevin. And did I miss—

DR. WINN-DEEN: A lot of help from the ex officios.

MS. CARR: And the ex officios have been enormously helpful and we keep—and we must keep badgering them to help us identify not only the gaps but the common sense solutions that can make the recommendations of the committee tangible and actionable by the Secretary.

DR. TUCKSON: Great.

MS. CARR: CDC, NIH, AHRQ, DVA has been on as well—Veterans Affairs has been on the pharmacogenomics task force—no, they haven't. Maybe they want to be. Maybe they don't want to be.

(Laughter.)

DR. TUCKSON: How did Sherrie get out of that that easy?

MS. CARR: Yes. But any other ex officio agency—

DR. TUCKSON: That was smooth.

(Laughter.)

MS. CARR: --can. We are planning to have an in person meeting of the task force in probably the very beginning of September where we can really have a revised draft—rather a draft report of the committee together by then and also have—prioritize the recommendations.

DR. TUCKSON: Okay. So I guess the challenge I'm sort of asking—and I'm going to turn to Suzanne who is very good at staffing these things—she's top notch. So you've got the examples, Suzanne. You said that at some point people can comment to you on the gaps in the yellow page literature review and analysis.

If they also wanted to inform some ideas for James to think of outside and the committee outside of the literature review, should they also send that to you or directly into James?

MS. GOODWIN: I think they can send it to me.

DR. TUCKSON: Definitely Suzanne. All right.

(Laughter.)

DR. EVANS: And my—I would just have one plea that anybody who happens to read it, my general sense is that we have a huge smorgasbord of issues and not that we're missing ones. I think that where we've been really successful is identifying a whole slew of things and I would just reiterate what I mentioned a minute ago. I think that recommendations get diluted when there are too many of them. So I would be most interested in what people think about what goes beyond the purview of this task force, what really doesn't make sense to address in the isolated context of pharmacogenomics, and try to focus. That's one of the things I think we have before us.

DR. TUCKSON: Well, with that, I really again want to thank you, not only Emily but the committee. This is good hard work worthy of our effort and I think that we've brought everybody up to

speed and so now we're ready to move to the next stage of this project.

Jim, I'm glad that you're able to take the baton.

With that, we are not bad actually. It's 4:05—really 6, but I'm going to give myself a leeway--4:06, and we will reconvene for another exceedingly important discussion on the large population study. We'll do it in exactly ten minutes, which makes it what—something like that—let's say 4:15. 4:15 right on the money.

(Whereupon, at 4:06 p.m., a break was taken.)

**LARGE POPULATION STUDIES SESSION**
**UPDATE ON SACGHS'S DRAFT REPORT ON THE POLICY ISSUES ASSOCIATED WITH UNDERTAKING AL ARGE U.S. POPULATION COHORT PROJECT ON GENES, ENVIRONMENT AND DISEASE**

DR. TUCKSON: Okay. Thank you for joining us and everybody is back on the committee. Can we focused again?

Now you know there was a technical glitch with the satellite otherwise you know I was ready to start exactly as promised at 4:15 so don't think that on break you guys can come back in late and I'm not running a tight ship. All right.

Now, in March of 2004, we identified large population studies as a high priority issue warranting our attention as the committee was reminded this morning when we looked at our list of strategic issues.

Our inquiry on this issue has also been shaped by a request from the NIH Director, Dr. Zerhouni, that we identify key policy issues associated with undertaking a large U.S. population cohort project on genes, environment and disease, and provide advice on the scientific—this is very specific language, especially for the new folks, I want you to lock in on this—provide advice on the scientific, public and ethical processes and approaches that might be used by HHS policy makers to make optimal decisions about undertaking such an effort. A draft report and recommendations were prepared—you might want to mute your mike for just a second in North Carolina. Thank you.

A draft report and recommendations were prepared and reviewed at our last meeting. I would like to thank Hunt Willard, chair of the LPS task force, and all the task force members, Sylvia, Chira, Kevin, Debra, Julio, Joseph and, the ex officios, Ellen Fox from DVA, Allen from NIH, and Maureen from CDC, for all their hard work in preparing and revising this draft to reflect our discussion at the March meeting.

A copy of that revised draft report is in tab 6 of your briefing books.

At our March meeting we also made decisions about the public comment process. I want to commend the task force for their efforts to make outreach as broad as possible. The draft report was released for public comment on May 22nd. This slide that's up right there gives you a sense of the efforts that have been made to solicit this public comment. The report along with a call for public comments was posted on the SACGHT's website May 22nd. You see the site. On the say day we mailed a "dear colleague" letter with the report to over 1,000 individuals and organizations. We notified selected media organizations to the NIH Office of Communication on June 7th. Last week we were happy to see in Science magazine a brief mention of the report. You'll find a copy of that in your table folders.

Announcements were also published in the Federal Register, the official government publication, and the NIH Guide for Grants and Contracts Notice, which reached a significant portion of the scientific community.

You'll find in your table folders a list of all the mechanisms that have been used to disseminate the report and the request for comments.

We have asked the public to submit their comments on the draft report by July 31, which means there is time to do more outreach. So if you all know somebody that we didn't get, somebody you think is important, the train, while it left the station, ain't completely gone where it's going.

I encourage everyone here and all of you participating via the web cast to submit comments. I urge you to stimulate interest in the report.

As we continue to the public comment solicitation in our efforts to identify the policy issues around large gene-environment projects, we thought it would be helpful to learn more about the environmental components of gene-environment studies. We are very happy that two experts are with us today to speak on this topic.

Dr. David Schwartz is the Director of NIH National Institute of Environmental Health Sciences and Dr. John Hewitt heads the Institute for Behavioral Genetics at the University of Colorado. Their biosketches are in your table folders.

Dr. Schwartz is joining us by video from North Carolina. His talk will help us to understand more about the environmental factors that would be a part of a large population project. He will help us to understand how those environmental factors are measured and what we are likely to learn from studying their interactions with genetic risk factors. He will also discuss some of the policy issues associated with measuring environmental exposure in a large scale study.

Dr. Hewitt will then focus on the social and behavioral factors in the environment and the way that these factors interact with genetic risks to affect health outcomes.

Dr. Schwartz, we really do appreciate your taking the effort and all of your people there at North Carolina who made it possible for the technology to work. With that, I would urge you to take yourself off mute and please share your thoughts on environmental components of gene-environment studies.

**ENVIRONMENTAL COMPONENTS OF GENE-ENVIRONMENT STUDIES**

DR. SCHWARTZ: Thank you very much.

(Slide.)

It's a pleasure to be here with the committee. I want to thank the committee for making time for me on their busy schedule.

Let me first say that I'm highly supportive of the report of the committee and I'm appreciative of the fine work that the committee has done in this regard.

There are four issues that I'd like to address during the brief time that I have on your schedule. One is I'd like to clearly establish the need and the importance of precisely measuring environmental exposures when considering susceptibility for a variety of diseases.

Secondly, I'd like to be able to demonstrate how the exposure biology program within the Genes and Environment Initiative takes some very important steps to develop these very precise measures of exposure.

Third, to show how the work in the Genes and Environment Initiative, and specifically the exposure biology program, can interface with the grander plans that the committee put forward in terms of the population-based studies.

And then, lastly, just reflect on some policy issues that are relevant not only to genetics but also environmental concerns when considering etiology of disease.

So I can't control the slides from this end but if I could have the next slide.

(Slide.)

This next slide I took from a publication of Francis Collins where he demonstrates the clear importance of the sequencing of the human genome in terms of understanding biology, physiology and how that physiology relates to a more clear understanding of disease and the distribution of disease in populations.

(Slide.)

No, go back.

(Slide.)

So the importance—well, it doesn't much matter but the issue is that our belief—a belief that Francis and I both share—is that focusing on environmental exposures when considering genetic risk

factors are a way of accelerating those discoveries, both the basic discoveries, as they relate to basic biology and pathophysiology, but also maybe more importantly in terms of etiology of disease.

Let me give you two reasons to consider environment when considering the etiology of complex human diseases. In an editorial, Walt Willett commented on the importance of environmental factors and behavioral factors in terms of the risk of developing many of the complex diseases that are faced by Americans and people all over the world.

(Slide.)

And basically what he illustrates in this slide is that between 70 and 90 percent of the etiology of major diseases in the United States are caused by reversible behaviors and exposures and in considering the etiology of these complex human diseases, less than five percent of the etiology of any one of these complex diseases, colon cancer, stroke, heart disease and diabetes are caused by single gene mutations underscoring the importance of considering environmental exposures.

(Slide.)

We've been looking at twin studies very carefully and basically what we have found is that when you look at many of the complex human diseases, such as asthma, diabetes, prostate cancer, breast cancer and Alzheimer's diseases, diseases where there are several—at least several twin studies to rely on, between 20 and 50 percent of the etiology of any of these diseases is caused by factors other than genetic factors. Largely being environmental factors, behavioral factors or nutritional factors that are critical in terms of the development of these very important disease processes.

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A second reason for considering environment in terms of understanding the etiology of disease is because environment can simplify the phenotype of these complex human diseases. For instance, in asthma the studies of generalized forms of asthma have demonstrated a genetic etiology of asthma. However, when you look at the loci throughout the genome or the genes that have been associated with the development of asthma, almost every single chromosome has a location on it that is associated with the risk of developing asthma.

(Slide.)

However, this is no real surprise when you consider the fact that multiple exposures account for the etiology of asthma and that asthma is a very complex biological process, and there are many phenotypes of asthma from the development of air flow obstruction to wheezing to the requirement of medications for the treatment of asthma.

(Slide.)

Now our belief is that if you break down asthma by etiologic variance and consider that house dust mite induced asthma—

(Slide.)

--is probably very different than ozone induced asthma, is different than endotoxin induced asthma—

(Slide.)

--you can use these environmental exposures as a way of creating a very narrow pathophysiologic phenotype that can then facilitate understanding the genes and the biology that underlie those important disease processes. In fact, this approach has been very successful in understanding specific aspects of human biology of disease pathogenesis, individual susceptibility, impact on prognosis and treatment, and also the distribution of disease in populations.

(Slide.)

Now with the support of Secretary Leavitt, Dr. Zerhouni, the other institute directors, Francis Collins and I developed a Genes and Environment Initiative. The basic approach in the Genes and Environment Initiative is to use genetic variation and also environmental variation as a way of understanding the etiology of complex human diseases and to focus that on understanding diseases of

important public health import. So the idea is to not only do whole genome association studies but combine those whole genome association studies with much more precise measures of exposure as a way of looking at the combined risk factors—these combined risk factors for the development of these complex human diseases.

(Slide.)

When you consider the precision of being able to measure genetic variation from one individual to the next and you compare that to what we're currently able to measure in terms of environmental history from one individual to the next or exposure history from one individual to the next, it's patently obvious that we need much more precise measures of exposure. So within the Genes and Environment Initiative we have developed an exposure biology program to do precisely that, which is to develop measures of exposure that reflect biological responses to classes of toxins or to measure biological responses to nutritional changes or activity levels that provide us with a much more precise estimate of the risk of going on to develop disease, and then to be able to measure the association between that risk and the genetic factors that place one at risk of developing disease.

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So then the idea is to--

(Slide.)

--is to develop these personalized biological measures of exposure that provide a level of precision that allows us to look at both genetic variation and environmental exposures in combination in terms of the risk of developing these diseases.

(Slide.)

One of the examples that I'd really like to focus on is that of hepatocellular carcinoma.

(Slide.)

We've known for many years that hepatitis B virus through the development of hepatitis and hepatic cirrhosis place individuals at risk of developing hepatocellular carcinoma.

(Slide.)

It has been recently appreciated by Jerry Wogan and John Groopman that exposure to aflatoxin through aspergillus flavus, a common spore that contaminates food especially in Southeast Asia, also places individuals at risk of developing hepatitis and also hepatocellular carcinoma.

(Slide.)

But it wasn't until they identified, and others identified, biomarkers of exposure to both hepatitis virus and also aflatoxin.

(Slide.)

And they relied on two specific biomarkers that they were able to then identify the relative risk--

(Slide.)

--of developing hepatocellular carcinoma that was contributed both by aflatoxin and hepatitis B, and also that they were able to appreciate the synergy between these two factors.

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One important issue is that if they went back to dietary history and they looked to see whether dietary exposure to aflatoxin was associated with the risk of developing hepatocellular carcinoma, they weren't able to identify a relationship here. This clearly demonstrates the importance of these biomarkers in terms of the risk of developing disease and demonstrates the importance of these biomarkers in terms of understanding how the dietary factor like aflatoxin contributes to the risk of developing disease. Something that they wouldn't have appreciated had they relied simply on dietary history.

(Slide.)

Another important factor is that it took them between 25 and 30 years to develop the epidemiologic evidence, the populations, the biomarkers and then to test those biomarkers in populations before they were able to come up with this association and go on to develop preventive strategies in terms

of preventing the development of hepatocellular carcinoma.

We believe through the Genes and Environment Initiative we'll be able to compress this time line so that we'll be able to identify the etiology of disease within a five year horizon.

(Slide.)

What can we currently measure? There are very important exposures in the environment that place individuals at risk of developing disease, polyaromatic hydrocarbons that are released by smoke and various forms of air pollution, particulates in the air, dietary factors and physical activity factors that we currently measure by questionnaire, monitoring of these substances in the blood, urine and air samples, as well as measuring these substances in DNA adducts and protein adducts.

(Slide.)

Next.

(Slide.)

This allows us to then see whether these factors are associated with a risk of developing various diseases of public health import.

(Slide.)

The problem is that this approach makes it very difficult to understand the mechanisms that underlie this association and this approach ends up being a poor predictive factor in terms of disease pathogenesis and progression.

(Slide.)

So the limitations of the current exposure data are that they rely heavily on questionnaire information and environmental assessments, not personal assessments. They lack sensitivity and specificity. They are qualitative and not quantitative, and they lack precision in a measurement assessment. They are environmental, not personal in terms of their exposure measurements in exposure assessment. And they don't address a contribution of diet or lifestyle in a quantitative fashion.

(Slide.)

In aggregate, what happens is this limits the power to make definitive conclusions about relationships between exposure and genes as well as these two risk factors and the development of human diseases.

(Slide.)

So then we think through the Genes and Environment Initiative that we'll be able to have a greater impact in terms of understanding the biological importance of this.

(Slide.)

By measuring the biological impact and developing indices that allow us to measure the biological impact and assess genetic susceptibility.

(Slide.)

In aggregate, what will happen is this will allow us to develop mechanistic linkages that are better predictors of disease risk.

(Slide.)

So there are two aspects to the exposure biology program within the Genes and Environment Initiative. One is the development of new technology, which we believe will take at least a four year period of time. A second is to adapt existing technologies to various exposures that are clearly important in terms of the risk of developing disease. We think we're going to be able to develop assessments of exposure that are personalized assessments of exposure but also assessments of exposure that tell us whether someone is biologically responding to those exposures. We believe that that's within the horizon of the Genes and Environment Initiative.

(Slide.)

And we think that these exposure assessments will allow us to have tools that will be available to studies such as the large population based study supported by the Secretary's advisory committee but we

think that these tools will also be accessible to other studies, case control and cohort studies that are interested in examining the importance of diet, nutrition--nutrition, diet, physical activity as well as a variety of environmental exposures.

(Slide.)

The policy considerations as they relate to environmental assessment are very similar to the policy considerations as they relate to genetic assessment because they address very similar issues that relate to privacy and confidentiality of data, and these are things that we need to seriously consider and figure out how to deal with in terms of protecting the privacy of our study subjects.

We need to foster public involvement in these studies both before, during and after the study and we need to keep in touch with the study subjects in a very clear way. We need to develop consensus policies for data access and sharing as well as public and private dissemination of the data and communication of the important study issues as they develop and as they come to fruition.

A very important issue related to these exposure assessments is we need to assess how the public is going to respond to these exposure assessments before we get involved in the very large population based study looking and examining the risks of environmental exposures in terms of the risks of developing various diseases.

So those are the comments that I wanted to make and I'll stay on the line for the question and answer period.

MS. CARR: Thank you, Dr. Schwartz. This is Sarah Carr. I'm the Executive Secretary of the committee and Dr. Tuckson, our chair, just stepped out for a moment. As you indicated, we're going to have the Q&A and we appreciate your staying on.

So we'll turn now to John Hewitt for a presentation that will focus on the social and behavioral components, and hopefully will complement Dr. Schwartz's presentation.

**SOCIAL AND BEHAVIORAL COMPONENTS OF ENVIRONMENT IN GENE-ENVIRONMENT STUDIES**

DR. HEWITT: Well, I thank the committee for the invitation to join you and share some thoughts with you.

(Slide.)

My invitation came very recently and so I didn't have a great deal of time to learn about the work of the committee, which I have to confess I wasn't aware of until just a few weeks ago. I read the public comment document since then and have been very impressed with it. But at the time of thinking about this and having been invited, I'm not entirely clear what the kind of audience was, I just thought, well, I better talk a little bit about what I know about and that's behavior genetics, and I'll just say a few things about that.

(Slide.)

Similar to what we just heard, when you look at the—almost any trait, and on this first slide body mass index, IQ is the kind of thing we study, alcohol use, depression, atopy which is going to asthma and eczema and things of that kind, heart rate, cholesterol, personality characteristics. If you look at pairs of identical twins, you are going to find that they correlate very highly or moderately highly for those traits. So we know that individuals who are genetically identical and are being reared in the same household tend to be fairly similar, although they are not actually identical. In fact, there are quite large differences even within that pair. So that suggests that there are environmental influences that differentiate between households in the etiology of all of these different kinds of variables.

If we then go and look at other pairs of twins who are not monozygotic twins and genetically identical but dizygotic twins are no more alike than brothers and sisters genetically, you find that the correlations typically drop down to about half what the monozygotic twin correlations were. Sometimes it's higher and sometimes it's lower but it's often around there. What that tells us if you're raised in the same household but you're not genetically identical, your genes are segregating and you're much less

similar than if you're an identical twin. If you put the two together you typically see this kind of relationship.

(Slide.)

When a behavior geneticist looks at those data, he talks about the genetic variation, which I'm not particularly interested in right now, but also the environmental variation. A behavioral geneticist typically starts off by saying, "Well, how much of the environmental variation that's causing differences in the population is shared by members of the family and making them all similar?" And this also includes if there's errors of measurement which are correlated, that would go in there. And how much of this environmental variation isn't shared by members of the families intends to make them different? And that would also include measurement error.

(Slide.)

This slide simply shows, before I pursue that line of thought, the relationship between correlation coefficients that I was just putting up on the board there, on the slide there, and the average difference you'd expect to find for a pair of individuals just chosen from that kind of grouping that had that kind of correlation.

If you just take a random pair of individuals from the population, what you expect for something like IQ, which has a standard deviation of 15, is a typical difference, which in a randomly chosen pair of individuals, one in California and one in New Jersey or wherever it would be, is slightly greater than the standard deviation of the population.

As the correlation rises, the typical difference for that kind of pair of individuals declines but what I really want to show you is something like this: If you have a correlation of about .4 for pairs of individuals, say siblings or individuals in a household, the typical difference—the absolute typical difference of a pair like that is still quite a large quantity compared to randomly chosen individuals in the population.

(Slide.)

So, as I say, behavioral geneticists divide things up into genetic influences and environmental influences, those that are shared by families and those that differentiate members of a family.

(Slide.)

And with some simple assumptions you can come to a conclusion about what's doing what.

(Slide.)

And the slide that was just shown at the beginning of the last presentation looking at the genetic and environmental partition based on twin studies for common disorders does this sort of thing in some sense. Typically, you find a large contribution from the genes for most traits, quantitative traits that we look at like body mass index or IQ or heart rate or personality, and typically you find a contribution of the environment. But what we find our kinds of studies is that a large chunk of that environmental variation differentiates members of the same household. Not all environmental variation is associated with differences between households.

(Slide.)

So individuals who share their family environment, which is indicated by "C" for common, and are genetically identical across the entire genome, that's monozygotic twins, are quite similar but they're not identical by any means.

Individuals who share their family environment but only half of their genes are somewhat similar but often very different.

Environmental differences within families may be as important as environmental differences between families.

(Slide.)

I want to give two brief illustrative examples. The first is body mass index. The second is substance use and abuse.

(Slide.)

Body mass index. This is data from the National Heart, Lung and Blood Institute. A twin study of obesity. It was published a while back. These are the same pairs of twins followed across their adult life. And these are the correlations for body mass index for identical twins, .8, .73, .72, .69 at the age of 63. These are the correlations for the dizygotic twins, non-identical twins, in that study, .4 something, .4 something, .3 something, .3 something.

There's also information in this study about the continuity of body mass index from one age to the next across the adult life span.

(Slide.)

The result of analyzing those data is that you can estimate the proportion of the variance in body mass index and decompose it into its genetic component and its environmental component, and you can estimate the proportion of that variation which is not shared by members of the twin pair. Now since these are adult twins, it's not surprising that the environmental influences aren't shared but it just makes the point again that if you're looking at environmental influences on a trait of interest, like body mass index, which is the direct underlying quantitative variable for obesity, then you need to take account of the fact that environmental differences between members of the same family are going to be just as important as environmental differences across families.

(Slide.)

And you can take advantage of the information of stability from age to age to decompose the genetic variance into that which is newly arising at any given age and that which is the total, and the same thing with the environmental variance.

(Slide.)

And all this really tells you is—and I'll look at the top first—there are substantial genetic influences on body mass index throughout adulthood and some of the genetic influences in middle age are independent of genetic influences in younger adults.

Individuals leaner for environmental reasons early in adult life are unlikely to sustain their leanness. That's because the environmental variation seems to be arising anew from age to age. So environmental influences may need to be chronic to be influential over long periods for a variable light body mass index.

(Slide.)

The second example is something that we study, which is substance use, abuse and dependence. Substance abuse is clearly a major health issue in this country and so we're interested in that.

(Slide.)

What we find when we look at substance use and the development of dependence, we find that both use and dependence are surprisingly—well, use is clearly common in adolescence but the development of dependence is also quite common in adolescence. By age 18, 70 percent of adolescence are experimenting with alcohol. One in three with marijuana. One in three with tobacco. One in ten with other illicit drugs. And one in five of individuals in our community surveys show dependence on some substance but it's often tobacco. We find few sex differences in substance use or dependence and we find an increase across the adolescent period.

(Slide.)

When we look at family resemblance for identical—MZ twins, who are identical twins, non-identical twins, ordinary siblings and adoptive siblings who are not biologically related, when we look at use of illicit drugs, we see a pattern that's consistent with genetic influences being relatively unimportant but family environmental influences being quite important.

(Slide.)

When we look at something like dependence, which is a much more severe form of the phenotype, which follows use, abuse, interdependence, we find a pattern of variation which is much more

consistent with genetic variation.

(Slide.)

So the point is that all aspects of substance use show family similarity. At least some of this is genetic but that's especially so for abuse and dependence.

(Slide.)

And in this slide I simply note the fact that when we're studying behaviors of interest, which will be risk factors for diseases, whether it be substance use, abuse and dependence or dietary factors or exercise factors, we need to be aware that the influence of the environment and the influence of genes may change during the developmental sequence.

(Slide.)

You can't measure the environment one time only and expect to get the answer to whether this is etiologically important or not.

(Slide.)

Well, what kinds of environments do social scientists measure? For this I just want to draw the committee's attention to the national longitudinal study of adolescent health, which is currently funded and lead by NICHD, because these people are social scientists who have enormous experience of measuring social and behavioral environmental influences.

(Slide.)

This slide simply shows the kinds of things that they have focused on. The characteristics of the school, the characteristics of the family, romantic relationships, neighborhood characteristics, community characteristics, peers, and the work environment.

(Slide.)

And on the next slide there are examples of the kinds of things that they've looked at under these general rubrics. The percentage of students who smoke in the school, the students who live with both parents, school cohesion, demographic composition, socioeconomic status. In the family the parents' health, the maltreatment of children as offspring in the family. In the neighborhood, crime, violence, poverty and so forth. And I'll move quickly through those and you have them on your handout.

(Slide.)

The view that I've just expressed is a fairly simply minded view of genes and environment contributing to outcomes. We know that that's way too simplistic a view and we need to worry about things like gene environment correlations, the effects of migration, interactions and so on down this list. Because of the time available, I just want to mention gene-environment correlation especially.

Epidemiological studies that measure environments and correlate them with outcomes are always going to be at risk of drawing invalid inferences if it is the case that the environments are correlated with differential genotypes. One thing that behavior genetics analyses tell us is that the genotype of the individual plays a role in selecting from the available environments so developing a gene environment correlation. This is particularly going to be of interest when you look at diet, nutrition, activity levels and so on.

There is an interaction. You do not impose a diet on an individual. You offer a smorgasbord of opportunities from which the individual chooses. Any study—a large scale population cohort study that's measuring genes and environment needs to make sure that the design and analytic strategy is open to that kind of interpretation.

(Slide.)

I want to finish with some lessons from the Lanarkshire Milk Experiment, which I think is something that every student of experimental or epidemiological design should read about. This was a study conducted in 1930 in the Scottish region of Lanarkshire. It was intended to be a randomized—almost a clinical trial of the efficacy of providing supplemental free milk to children as opposed to not providing it and what was the impact of that on growth.

It was a study of 20,000 children in Scotland and they were—the intention was to randomly assign schools to having a pasteurized or raw milk and then the teachers were to randomly assign the individuals within the school to receive the milk or not, and then the study followed the height and weight growth of those children.

Unfortunately, with the best intentions the randomization was not perfect and there was introduced a confounding between assignment to the milk receiving group and assignment to the group that did not receive milk. Some leeway was left for the individual schools to say, well, we have done the random process, it doesn't look quite right, you haven't got it quite right, we can do some reassignments, and unconsciously there was apparently an assignment of needier children to the milk receiving group, which invalidated the results of the study.

(Slide.)

But what Stuydant (ph) pointed is that his conclusion was that had this study been conducted on 50 pairs of identical twins, one randomly assigned to the milk condition and one not, there would have been equivalent power to detect the nutritious effects of the milk and the experiment could have been much more tightly controlled. He concluded that identical twins are probably better experimental material than is available for feeding experiments carried on other mammals and the error comparison between them may be relied upon to be so small that 50 pairs of these will give more reliable results than the 20,000 with which we've been dealing. That is an overstated case unless the correlation for the outcome measures is very high.

But Stuydant, the statistician, was drawing attention to the very considerable addition advantages of the experimental control that can be exerted than working with a small number of closely matched pairs whose only difference is the experimental treatment.

(Slide.)

In the case of a large cohort study you—we're not going to be assigning MZ pairs randomly to one condition or another but they do still provide the best matched pair control controlling for genotype to look at the effects of the environment. These effects of the environment will be environmental effects that differentiate members of the same family but, as I've said, it appears that these are quite likely to be very important sources of environment.

(Slide.)

So my thought for you to consider as a committee is whether the experimental design of this large—very large population cohort study of genes to environment might not be enhanced by a deliberate systematic sampling of genetically identical pairs of twins who could be assessed probably in much greater detail given the cost efficiency of the small *n* benefit for a very detailed study of the environment. So using the identical twins to study the environment. That gets around the confounding of the gene-environment correlations that are typically found in large scale region to region differences, for example.

(Slide.)

My conclusions are environmental influences differentiate members of a family as well as making them similar. Gene-environment correlations caused by family genetic variation, migration, environmental selection complicate the interpretation of epidemiological studies of environmental influences.

(Slide.)

The influence of the environment may be different at different stages of development and transitory environments compared to chronic ones may often have transitory effects but, by comparison, genes, of course, are a chronic influence.

Social scientists have long experience of the assessment of environmental influences on behavior and health, and I recommend that you contact someone like Kathie Mullan Harris who is the director of the National Longitudinal Study of Adolescent Health, who is an expert in these kinds of measures.

(Slide.)

And my final recommendation is for you just to consider the possibility of enhancing the design while incorporating a deliberate sampling of MZ twins with extensive assessments of the environment that may provide a powerful efficient well-controlled design for the study of the environmental influences and, incidentally, the study of gene-environment interactions.

Thank you.

DR. TUCKSON: Thank you, both, very much.

And now to lead our discussion, let me turn to our colleague, Julio, who will take us through this.

You're still with us in North Carolina? Are you okay?

DR. SCHWARTZ: Yes, we are.

DR. TUCKSON: You can hear us okay?

DR. SCHWARTZ: I can.

DR. TUCKSON: Thank you.

**Q&A**

DR. LICINIO: So the floor is open for questions. Before we—I'd like to start with one question to Dr. Hewitt about how to assess the family in a shared environment because that, I think, is probably the biggest limitation because the toxin-like components, you can always measure them chemically but how do you—how would you suggest in a very large study of a million people assessing shared environment?

DR. HEWITT: Yes. I don't think those are necessarily different kinds of environments. That's a statistical decomposition into, between and within. And how do we assess it? It's assessed statistically in terms of its consequences for similarity. The most direct way, for example, is to look at pairs of individuals who are genetically unrelated that have been reared in the same home to the extent that they correlate positively for a trait of interest that indicates the impact of the environment they've been sharing. How to assess it in terms of what are those environments is presumably then the question that you want, and I don't think those environments are necessarily different. It's not that they are different components of the environment. It's just that they aggregate or differentiate so it's measuring the same environments. The point—my point really is that what we've learned about the extent to which these environments aggregate in the families or differentiate members of the family suggests to us that you will learn a lot about the available environmental range by studying differences between individuals even when they are from the same family.

DR. LICINIO: But let's say in terms of the large study which would be across a million people in several states, how do you measure like psychosocial environmental factors? Are there any kind of batteries of tests you would suggest? What do you assess?

DR. HEWITT: Okay. Well, there are things that are known to be associated with the behaviors that I'm interested in and they are usually characteristics. So parental psychological disorder, parental substance use and abuse, parental style. The treatment of children has turned out to be a very robust predictor of poor behavioral outcomes. So the mistreatment of children. And those things can be assessed by questionnaires and interviews. Both of the parents of children and of the children retrospectively themselves. So that's one class of variables but they are going to be done by interview assessments.

Another class of variables are background variables to do with the school characteristics, the neighborhood characteristics and community characteristics, which can be done at various levels through databases from census tracks and so forth.

DR. SCHWARTZ: I was wondering if I could add to that answer? So one area that we're very interested in exploring is in the Genes and Environment Initiative and the exposure biology program is to develop the biological markers of response to various forms of stress. We intend to focus on a variety of biological pathways such as oxidant induced stress or specific inflammatory responses or even transcriptional markers as a way of trying to identify how biology is altered by various environments, including behavior.

So while we may not be able to specifically identify the exposure or the behavioral stress, we may be able to identify the biological fingerprint that places an individual at excess risk of developing a disease given a specific genetic susceptibility.

DR. TELFAIR: This is a question for both of the guest speakers. One of the issues, and there is many of course but one of the issues that came up in the work for this project was a utility question and it's a utility question in light of the need to be able to prioritize what the study—what to really focus on given that there may be limitations in resources and time, and that sort of thing.

So I would like to see from your perspective, given that you focused on this, what do you see if you had to make some direct recommendations to focus? What would you think would be critical to look at given your perspective?

Sorry about the feedback.

(Laughter.)

And we're not in Colorado either.

DR. HEWITT: Well, okay, I'll go first since I'm here. It clearly depends on the outcomes which you're most interested in and the interests that I have aren't necessarily the interests that this overall project has. I was just speaking from my experience.

But I have to say that I gave the example of BMI which clearly is something which is related to a wide range of diseases, common diseases, and in that case I would endorse a focus on diet and physical activity, and all of those things that have been characterized as a toxic food environment. That will be an enormously interesting thing, availability of resources for activity and exercise, the saturation of different kinds of fast food versus healthy foods, and so those kinds of things would be enormously interesting and probably productive for the study of obesity and heart problems, diabetes and so on.

It would also be enormously instructive in the context of the kinds of design issues I was talking about to include a focus on individual behavior and individual selection of the environments which are offered to people. I think that would be very helpful so that's one area.

The other kinds of things that I'm interested in are more psychological disorders, substance use and abuse development, and for those things exposure and availability of substances would be very important but they may not be the things that are of most interest to this committee.

DR. TELFAIR: Thank you.

DR. SCHWARTZ: I think in terms of utility there are two components, at least two components that we'd like to affect. One is we have the opportunity by identifying specific environmental exposures that are relevant to the risk of developing disease to decrease the risk of developing disease by altering exposure to those environmental agents. Right now we don't have as much information as we really need to do that.

Second, and I think equally important, I believe that by defining the environmental and genetic risk, we'll be able to understand disease pathogenesis at a much more precise level. By understanding the basic mechanisms of disease, I think we'll have a terrific opportunity to identify disease at a much earlier stage. I think we'll have the opportunity to identify novel mechanisms that may lead to new cures and I think that we'll be able to embark upon interventions of a secondary preventive nature where we know the disease has started but we think that early treatment may avert the full blown development of disease.

DR. TELFAIR: Thank you.

DR. LICINIO: Go ahead, Kevin.

DR. FITZGERALD: Yes. I would like to thank both speakers and ask both of you also in the presentations that you made if you look at other nations that have national databases and things, is there anywhere proof of principle precedent for the kinds of things that you want to do? In other words, have they been done somewhere else to some success, the various sorts of things that you're suggesting we might do?

DR. SCHWARTZ: Well, I can answer that just in the context that there is proof of principle that

specific exposures and specific gene changes are associated with the risk of developing disease or the likelihood of preventing disease from occurring. So clearly genetic factors in combination with environmental exposures have been shown to either be protective or detrimental in terms of the development of disease in terms of looking at variations related to TOL receptors that are important in terms of innate immune signaling. It's clear that some individuals with polymorphisms of these receptors are protected from developing asthma that is caused by exposure to these—exposure to bacterial toxins.

It's also clear, as I mentioned in my presentation, that biomarkers of exposures provide a much more precise measure of exposure that allows you to uncover the relationship between exposures and various disease outcomes.

DR. FITZGERALD: I'm sorry. I wasn't very precise in my question. I was more focused on the interaction that you were talking about between your GEI and the large population base studies. Has that been done and what results have come of that?

DR. SCHWARTZ: Not to my knowledge.

DR. HEWITT: But in terms of large scale national studies of pairs of twins, for example, there are a number of good examples in the European countries. Finland has a national registry. Norway, Sweden, Denmark and so on. But I don't think there has been a combination of the large scale population cohort studies with those things on the kind of scale with the kind of opportunity that you're talking about now.

DR. SCHWARTZ: So what I would just add to that is that the tools that are being developed in the GEI and are being tested in the GEI will be directly applicable to a large scale study in the United States as well as large scale studies around the world. And, as I mentioned in the presentation, will be applicable to even small scale studies in terms of other cohorts or other case control studies that are trying to identify the relationship between exposures and genetic variations in terms of the risk of developing disease.

DR. LICINIO: Additional questions?

DR. RANDHAWA: Just one question for my own edification here. So I'm trying to think of the clinical and public utility of the information that we will get and let's take BMI as an example. If you were to get more information that certain individuals with certain genotypes have a 1.5-fold increased risk or a two fold increased risk, what will be doing differently from what we have right now? Would we recommend people to be exercising regularly, eating the right diet? So for people who don't have the high risk genotype, would we say don't do that? And for people who do, are we going to say do it more intensely? What are the other interventions we think we will get once we know this information?

DR. HEWITT: Again, since I am here I'll go. It sounds like a policy issue to me.

(Laughter.)

But presumably at the genetics side, and we were talking about the environment, at the genetics side the intention would be to develop pharmacological interventions that might help control the behaviors that lead to obesity, which are conditional in the genes. That has been the story with leptin as something which has tried to inform the mechanistic understanding that would in turn lead to some changes that one could develop pharmacologically. It hasn't been successful with leptin but that's the intention.

But from the environmental side there is this issue that is unresolved as far as I know as to what it is that you can change in the environment to actually make a difference. At the moment we all know that exercise is—I mean milk is good for children. We know that but trying to demonstrate that it has a specific effect is a different issue.

As far as I know it's not clear. No one has come up with an environmental intervention yet that really makes a difference in the issue of obesity.

DR. SCHWARTZ: That was great, John. I would just add that it's also a matter of—so these healthy lifestyle issues are going to be recommendations regardless of what comes out of the study as

long as what we think is healthy remains healthy in terms of these behavioral interventions. But what this study and this approach will do is it will allow us to effectively target populations for more intensive intervention and I think that that is very possible because that is very important because these intensive interventions have been shown to have a big effect on behavior if you look at behavior or if you look at life style changes, if you look at cigarette smoking, if you look at issues related to physical activity. These much more intensive interventions are very effective in altering behavior.

DR. LICINIO: Any additional questions?

I had one question about the size of the study which is supposed to be like one million people. Does it make—especially the environmental factors very difficult to assess? Because like if you go to the point of it's better to do like a smaller study that is well controlled. If you have people from like all over the country it's very different backgrounds and social economic situations. Just in terms of like measuring them in a way that's consistent across these different settings I think is very challenging.

DR. HEWITT: Yes. I mean obviously I was making the argument for enhancing or complementing the large scale study with a more focused study with controlled genotypes in the case of MZ twins but there's good experience of large national studies, not this large. Again the AD Health Study is one example with a focus on psychosocial, environmental and social environment variables, and it can be done very well.

There's always going to be, as you all know, the compromise between detailed assessments and the number of assessments that you do, which is why it might be worth considering in my view the large study, yes, but also additional components that might provide efficient additional ways of getting at the information.

DR. LICINIO: Even though it's a much more homogeneous—go ahead.

DR. SCHWARTZ: I would also—is it okay if I talk?

DR. LICINIO: Yes.

DR. SCHWARTZ: I would also add that that's why the Genes and Environment Initiative and the exposure biology program within the Genes and Environment Initiative is so important because part of this program is to develop the environmental sensors and the biological response indicators that not only more precisely measure exposure and response to exposure but are tested in larger populations so that we can understand how feasible it is to use them in a large scale study involving a population even as large as a million individuals.

DR. LICINIO: The point I was going to raise before is that there have been these very large birth cohort studies. I'm thinking like right now of the one that was done in the northern most part of Finland and people were followed for many decades. Do you have any kind of—how informative was that in terms of environmental contributions since there was such a controlled set up? Are you familiar with those?

DR. HEWITT: I am not. I don't know.

DR. SCHWARTZ: One of the problems is a lot of these large studies have not collected personal measures of exposure and some don't even have the samples that could be used for personal measures of exposure. I think that study that you're referring to has that problem that it doesn't—it did not assess exposure adequately.

DR. LICINIO: Are there any additional questions or comments?

DR. TUCKSON: I am just running the train here.

DR. LICINIO: Okay. So, if not, I'd like to thank both of you and let Dr. Tuckson continue here.

DR. TUCKSON: Really again on behalf of all of us on the committee, both, David and John, thank you very, very much. You have added significantly to the committee and I'm glad that Julio was able to take us through that.

To let everybody understand the process here: We will take these comments and roll them into the other public solicitation of comments that we are getting, and we will be well informed by all of these

perspectives as we go forward.

Again, I remind you all if you have friends, neighbors and relatives that need to comment on the draft report, you've got the web site and all that stuff and you know how to just get them to get those cards and letters coming.

Here's the deal: We convene tomorrow at 8:30. For those who are at the DoubleTree, the shuttle picks us up in the lobby at—what time?

DR. : 7:30.

DR. TUCKSON: 7:30. How come you all know and I don't know?

(Simultaneous discussion.)

DR. TUCKSON: Thank you, Joseph. One for Joe. All right. Pay back, though.

So 7:30 in the lobby.

Now here's the deal. You're on your own for dinner and so we expect you to be on your best behavior because you're representing all of us.

(Laughter.)

See you tomorrow. Thanks again.

(Whereupon, at 5:29 p.m., the proceedings were adjourned.)

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