

**U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES{PRIVATE }**

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

Ninth Meeting

**Monday,
March 27, 2006**

Conference Room 6, Building 31C
National Institutes of Health
31 Center Drive
Bethesda, Maryland

IN ATTENDANCE:

Chair

Reed V. Tuckson, M.D.
Senior Vice President
Consumer Health and Medical Care Advancement
UnitedHealth Group
MN 008-T902
9900 Bren Road East
Minnetonka, MN 55343

Members

Sylvia Mann Au, M.S., C.G.C.
Hawaii State Genetics Coordinator
Genetics Program
Hawaii Department of Health
741 Sunset Avenue
Honolulu, HI 96816

Cynthia E. Berry, J.D.
Partner
Powell Goldstein LLP
901 New York Avenue, N.W., 3rd Floor
Washington, D.C. 20001

Chira Chen
1315 5th Avenue
San Francisco, CA 94122

James P. Evans, M.D., Ph.D.
Associate Professor of Genetics and Medicine
Director of Clinical Cancer Genetics and
the Bryson Program in Human Genetics
Departments of Medicine and Genetics
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7624

Debra G.B. Leonard, M.D., Ph.D.
Vice Chair of Laboratory Medicine
New York Presbyterian Hospital, Cornell Campus
Room F715, Mailbox 79
525 East 68th Street
New York, NY 10021

IN ATTENDANCE:

Julio Licinio, M.D.
Professor of Psychiatry and Medicine/Endocrinology
Neuropsychiatric Institute
David Geffen School of Medicine at UCLA
University of California, Los Angeles
Gonda Center, Room 3357A
695 Charles Young Drive South
Los Angeles, CA 90095-1761

Agnes Masny, R.N., M.P.H., M.S.N.
Adjunct Assistant Professor of Nursing
Temple University College of Allied Health Professionals
Research Assistant and Nurse Practitioner
Family Risk Assessment Program
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111

Joseph Telfair, Dr.P.H., M.S.W., M.P.H.
Associate Professor
Department of Maternal and Child Health
School of Public Health
University of Alabama at Birmingham
1665 University Boulevard, Room 320
Birmingham, AL 35294-0022

Huntington F. Willard, Ph.D.
Director
Institute for Genome Sciences and Policy
101 Science Drive, CIEMAS 2379
Box 3382
Duke University
Durham, NC 27708

Emily S. Winn-Deen, Ph.D.
Vice President
Strategic Planning and Business Development
Cepheid
904 Caribbean Drive
Sunnyvale, CA 94089

IN ATTENDANCE:

Ex Officio MembersAdministration for Families and Children

Martin Dannenfelser
Deputy Assistant Secretary for Policy and External Affairs
Administration for Families and Children
370 L'Enfant Promenade, S.W., Suite 600-W
Washington, D.C. 20447

Agency for Healthcare Research and Quality

Gurvaneet Randhawa, M.D., M.P.H.
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality
540 Gaither Road
Rockville, MD 20850

Centers for Disease Control and Prevention

Linda Bradley, Ph.D.
Office of Genomics and Disease Prevention
Centers for Disease Control and Prevention
4770 Buford Highway
Atlanta, GA 30341

Centers for Medicare and Medicaid Services

James Rollins, M.D.
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Department of Commerce

William Koch, Ph.D.
Deputy Director of Chemical Science and Technology
National Institute of Standards and Technology
100 Bureau Drive
Gaithersburg, MD 20899

IN ATTENDANCE:

Department of Veteran Affairs

Ellen Fox, M.D.
Director
National Center for Ethics in Health Care
U.S. Department of Veteran Affairs
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Food and Drug Administration

Steven Gutman, M.D., M.B.A.
Director
Office for In Vitro Diagnostic Device
Evaluation and Safety
Food and Drug Administration
2098 Gaither Road, MSC HFZ 440
Rockville, MD 20850

Health Resources and Services Administration

Linda Johnston-Lloyd, M.Ed.
Senior Advisor
Center for Quality
Health Resources and Services Administration
Parklawn Building
Rockville, MD 20857

National Institutes of Health

Francis S. Collins, M.D., Ph.D.
Director
National Human Genome Research Institute
National Institutes of Health
Building 31, Room 4B09
31 Center Drive, MSC 2152
Bethesda, MD 20982

Office for Civil Rights

Robinsue Frohboese, J.D., Ph.D.
Principal Deputy Director
Office for Civil Rights
200 Independence Avenue, S.W., Room 515F
Washington, D.C. 20201

IN ATTENDANCE:

Office for Human Research Protections

Bernard Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Office of Public Health and Science

Bernard Schwetz, D.V.M., Ph.D.
Office of Public Health and Science
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Executive Secretary

Sarah Carr
Secretary's Advisory Committee on
Genetics, Health, and Society
NIH Office of Biotechnology Activities
6705 Rockledge Drive, Suite 750, MSC 7985
Bethesda, MD 20892-7985

C O N T E N T S

	PAGE
Call to Order and Opening Remarks	
Reed V. Tuckson, M.D. SACGHS Chair	9
Large Population Studies Session	
Overview of Large Population Studies: Policy Issues and Possible Approaches	
Huntington F. Willard, Ph.D. Chair SACGHS Task Force on Large Population Studies	19
Full Committee Discussion	
Facilitator: Huntington F. Willard, Ph.D.	29
Next Steps	
Facilitator: Huntington F. Willard, Ph.D. and Reed V. Tuckson, M.D.	60
Pharmacogenomics Session	
Update from the Pharmacogenomics Task Force	
Emily Winn-Deen, Ph.D. Chair, SACGHS Task Force on Pharmacogenomics	64
FDA Draft Guidance for Industry and FDA Staff on Pharmacogenetic Tests and Genetic Tests for Heritable Markers	
Steven Gutman, M.D., M.B.A. Director Office of In Vitro Diagnostic Device Evaluation and Safety, FDA	70
Full Committee Discussion	
Facilitator: Emily Winn-Deen, Ph.D.	74

C O N T E N T S

PAGE

Public Comments

Gail Javitt, J.D., M.P.H.
Johns Hopkins University

85

Pharmacogenomics Session

Development of Recommendations

Facilitator: Emily Winn-Deen, Ph.D.

89

P R O C E E D I N G S

(9:02 a.m.)

DR. TUCKSON: Good morning, everyone, and welcome to the ninth meeting of the Secretary's Advisory Committee on Genetics, Health, and Society.

I know everybody sort of does know everybody, but just for the sake of it, I want to just go around again and have everybody just reintroduce themselves and their organization or affiliation.

I'm Reed Tuckson, a physician and senior vice president of UnitedHealth Group.

Going around to Sarah.

MS. CARR: I'm Sarah Carr. I'm the executive secretary of this committee.

DR. WILLARD: Hunt Willard, director of the Institute for Genome Sciences and Policy at Duke University.

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

DR. ROLLINS: Jim Rollins from the Center for Medicare and Medicaid Services.

DR. GUTMAN: I'm Steve Gutman from FDA.

DR. KOCH: William Koch, deputy director of chemical science and technology at NIST, Department of Commerce.

MS. BERRY: Cindy Berry, partner in the law firm of Powell Goldstein.

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

MS. AU: Hi. I'm Sylvia Au. I'm the state genetics coordinator at the Department of Health in Hawaii.

DR. TELFAIR: Joseph Telfair, associate professor, University of Alabama at Birmingham.

MS. CHEN: Chira Chen. I'm a patient advocate and also a researcher at UCSF.

DR. LICINIO: Julio Licinio. I'm the head of the Center for Pharmacogenomics at UCLA, and beginning May 1st, I'll be at the University of Miami.

DR. BRADLEY: I'm Linda Bradley from the CDC.

DR. COLLINS: Francis Collins. I'm the liaison member from NIH.

DR. SCHWETZ: I'm Bernard Schwetz, the director of the Office for Human Research Protections, and I'm also here representing Cristina Beato from the Office of Public Health and Science.

DR. LEONARD: Debra Leonard, vice chair of laboratory medicine at Cornell Medical College.

DR. SHAMANSKI: Fay Shamanski. I'm staff for the committee.

DR. WINN-DEEN: Emily Winn-Deen, vice president for business development and strategic planning for Cepheid.

DR. TUCKSON: Thank you very much, and I'll introduce some of the staff folks in a minute.

Thanks to all the guests who are around the table. I'm sure we'll be hearing from many of you at different points during the day.

Before we begin, let me thank Cindy Berry for serving as acting chair at the October meeting. I understand you've done such a terrific job that nobody likes me anymore. So thank you very much. We had an unexpected death in the family, so I really did appreciate your stepping in at the last second.

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 through the webcast.

By the way, committee, you are on camera and you should be on your best behavior, Joe.

(Laughter.)

DR. TUCKSON: I thank all those who are tuning in for their interest in our work.

As you know, we arrived at our study priorities through a systematic priority-setting process that we completed back in March of 2004. I think Sarah is trying to get those priorities up.

I'm sort of fanatical about starting every meeting with this review of our strategic process. I think that it is important that the committee sort of take a look at this, and it's up on the screen now. At the end of the second day, I want us to sort of relook at this again and revisit this. It is, to me, as your chair, important that I am advocating and pushing hard that your priorities are being addressed. But, of course, from time to time, we need to stop and relook at our priorities and seeing are these the priorities that we want, where are we, is it time to move some things off and some things up. So I think it is very important to take moments to reassess where we're going and how we feel about where we are.

Sarah, would you take us through that?

MS. CARR: Sure. As you said, Reed, in March of 2004, the committee identified 12 high priority issues, and they're listed in the column going down. And, by the way, you went through this fairly extensive and systematic process to get to these 12, and you also organized them into three categories.

The first was issues that you thought required only short-term action or monitoring, and those are the first four listed here because the vision statement is actually just a report of your priorities actually.

And then the second category was high priority issues requiring in-depth study, and they are listed here.

And then the third category was issues that had a more overarching aspect and required sustained action. On these issues, access, public awareness and understanding, and genetic exceptionalism, you have wanted to incorporate those issues in all of the reports and letters that you prepare for the Secretary.

Going across here is time. This sort of represents the life of the committee, really. And after you identified these priorities here, there was a number of things you've done. You sent a letter to the Secretary. Actually, your very first action was a letter on genetic discrimination after your very first meeting. Then you sent another one in March of 2004. And on genetic discrimination, we also did a letter in May of last year, along with a legal analysis, an analysis of the adequacy of current law. You prepared a DVD of personal stories of testimonies you heard in the fall from people who are concerned about genetic discrimination. And we also had done a wider solicitation of public comments, and those were pulled together in a compendium that you sent to the Secretary. So there were three things that went with that letter, the DVD, the compilation of public comments, and the legal analysis.

And after that, we've been having updates, and we'll have another one tomorrow on the status of federal legislation in this area.

On genetic education and training of health professionals, we had a roundtable session in October of 2003, and then you prepared a resolution that made nine recommendations in this area to the Secretary.

On patents and access, once we realized that the National Academy -- and Debra is going to go through all this tomorrow -- was doing a fairly extensive report on this issue, we decided to defer further action until that report was completed. So tomorrow we will be discussing that report and what, if any, steps to be taken by the committee.

On oversight, we had a roundtable in October of '03, and we've been in sort of a monitoring mode. This issue, obviously, also relates to the one on direct-to-consumer marketing. It has an oversight aspect.

I'll move down to the coverage and reimbursement. We had a lot of activity on that, and it has culminated in the issuance of our report today.

Large population studies. We've started work on that in a very serious way in actually, I guess, March of last year. We had a day-long session, an update in June, and then another day-long session in October. I'm just going to go through a lot of that, and today we'll be looking at a draft report and some possible ways to move forward with this.

On pharmacogenomics, we started work on that in June '05 and had a pretty extensive session then and an extensive last October, and we'll be talking about that quite extensively today.

On direct-to-consumer marketing, we wrote a letter in March of '05, another one more recently, and Reed will be talking about that in a moment.

On access, these are the issues that we are trying to touch on in everything we do. We did one letter that sort of relates to the access issue, and that pertains to electronic medical records and the effort to develop a national infrastructure to facilitate transmission of medical information, and Reed will be talking about that letter in a minute.

Then on public awareness and understanding, we have been trying to incorporate that issue into all of our reports and recommendations, and we wrote a letter about the family health initiative of the Surgeon General in June of last year. We sort of put that in that category.

Then on genetic exceptionalism, we have also been trained to attend to that in everything we do.

DR. TUCKSON: Thank you very much, Sarah.

I think that if you will just take a sober look at our progress here, I think what it shows is that as a committee you have been very focused and you have been very active. You have accomplished a great deal in checking off a number of these boxes. There are some that you will be able to check off, significant work, by the end of these two days. So I do hope that you will feel good about the fact that you don't just come here and have these intense meetings and nothing happens, that you are moving forward.

Now, there are certain things we would like to have more progress about. I think we all would feel better if we could say and point to, because of our efforts, genetic discrimination was resolved and that there was a bill in the Congress. Well, I'm not going to put that as my definer for our committee having scored a touchdown, because we just don't control that. But I think that we have been extremely active and vigorous. I'm not trying to pat ourselves on the back, but I think that we have at least kept to our strategy of trying to do things that are productive and helpful in these areas.

There's one that I would want you all to think about and I want to revisit. I'll just tee it up and we'll discuss it at the end of the session tomorrow. But that is the public understanding.

I'm still not sure I know enough anymore about today's world where the public is in terms of understanding these issues and whether or not there's more that needs to be done, whether we should be the ones to do it. But I've got that high in my mind as an issue for us just to be thinking about. So I'll just put that there for you to think about.

Since our last meeting, the coverage and reimbursement report was finalized and transmitted to the Secretary. Today marks the release of the final report to the members of the public. Give ourselves a round of applause.

(Applause.)

DR. TUCKSON: Because that's actually pretty cool.

We are going to be actively disseminating the report through a number of mechanisms. Can you put that slide forward?

Now, the deal is that we're transmitting it to the Secretary and their senior leadership. We did that in February. It is now posted on the website. E-mail announcements went to our distribution list of approximately 1,000 individuals, individuals who represent organizations, not just Bob Smith at 1309 Maple Street. A targeted mailing to about 150 individuals and organizations, including, as you see, the expert presenters, Genetic Counseling Services Group, public commentators, and key staff. Also key organizations who asked for it have gotten it. The HHS offices, patient advocacy groups, providers,

health plans. AHIP certainly is going to be helpful in that regard. AHIP is the Association of Health Insurance Plans and also Blue Cross/Blue Shield Association. Lab groups, technology assessment groups, and interested academics.

Now, the one thing that's not there is you. So what I need you to be thinking about is who do you think this ought to go to, and you should take certain leadership in making sure that you get this thing out to all the places that you think it needs to go. Don't be shy about calling people up and talking about it because we think it's pretty important.

We are working through the process of a press release to let the world know. That's complex when you deal with government. But I think that we actually may be able to have a press release, and we may even be able to talk about it before we leave here at this meeting. If not, it will happen right after the meeting. We'll keep you informed, but do be aware that we're not taking a passive role. This was a lot of years of our lives to get this darned thing done, and we're not going to just say, okay, we did a report. Which shelf do we file it on? That's not the purpose of this. So it's getting out and we're going to push it very hard. So I urge each of you to become a committee of one and make this important and disseminate it.

Any questions on the dissemination of that report?

DR. WINN-DEEN: I noticed on the list of people we're extending this announcement to, a category that said "expert presenters." Is there a thought to preparing a slide set that at least has the recommendations on it?

DR. TUCKSON: That's a great thought.

MS. CARR: Say that again. Sorry.

DR. WINN-DEEN: Well, we have a series of a dozen recommendations. Could we have a set of slides made that has those recommendations?

MS. CARR: Oh, so that you can present. Absolutely, that's a great idea.

DR. WINN-DEEN: And just put it up on the website.

MS. CARR: And then you can use it when you need it. Sure.

DR. WINN-DEEN: Or whoever we're targeting in the "expert presenters" category.

MS. CARR: Oh, I see.

DR. WINN-DEEN: Anything you can do to make things easier for them helps.

MS. CARR: That category represents the people we heard from and consulted with in-depth. But that's a great idea, Emily.

DR. TUCKSON: That's a deliverable.

Any other quick thoughts on that?

DR. LICINIO: Yes, I had a quick thought, which is that can the report in full, or at least parts of it, be available on the website?

DR. TUCKSON: It's on ours. So thank you for that, Julio. It is on our SACGHS website, which anybody can go to to get. So absolutely let people know that.

DR. LEONARD: Has this been distributed? I didn't see industry like IVD companies. I don't know if BIO is the right group or AdvaMed. They would be interested in this as well probably.

MS. CARR: Suzanne, are they on our listserv? They are, aren't they? We'll make sure they get it if we haven't done it.

DR. TUCKSON: That is a great thought. Thank you.

DR. LEONARD: And the second question. The Secretary has vetted this somewhat or got it in February. Do we anticipate when we will be hearing response at each implementation of recommendations or responses to them or anything like that?

MS. CARR: Well, we're aware that the report is being looked at within the Department. We've gotten some calls from some of the staff to the Secretary about it. So we hope to hear soon.

But may I say, I think it's a fairly complex set of recommendations and we don't want to rush them, I don't think, in terms of looking at it. So I think the longer they take -- well, to a point, but clearly they need to think about some of the cost implications and some of the other issues in the report.

DR. TUCKSON: But I think the key thing, Debra, there is that -- and I think it falls in some ways to me -- to make sure that on this and other areas, when we send these things forward, to try to figure out how to make this a higher priority or a priority within what the Secretary is doing. So we know they got it. We know they're looking at it and so forth.

Let me just say we're going to come to that in a second. I'll just go ahead and fast forward to this. One of the things that we are aware of from your evaluation reports is that we sort of felt like you want to know more about is anybody paying attention to these recommendations in the Secretary's office.

I think that Secretary Leavitt has had a chance now to be on the ground and get established. He still is fairly new, even as of our last meeting, and then was hit immediately with not only the ongoing bioterrorism issues, but then with the bird flu challenge, and then also with his own initiative, which is the health information technology initiative, which is occupying a lot of his priority. Those three are pretty big items.

I have had the chance to spend face time with him in actually all three of those areas, and so I've had a chance to see him out and about multiple times. I am going to try to see if I can't have the opportunity to chat with him or somebody on his staff a little more. Every time I see him, I always say, by the way, I bring you greetings from your advisory committee. So every time he sees me, I think he knows I'm going to say something about the Secretary's Advisory Committee on Genetics.

But I have not had a chance to sit down with him in any depth to go over all of our portfolio, and I don't know if any advisory committee chairman does get a chance to go over their portfolio in any depth with the Secretary. But I'm going to try to do that.

We got into the same issue with Secretary Thompson, and we were even trying to think about should we create or urge there be some coordinating person within his office. And that got us into all kinds of entanglements as it looked like we were potentially creating more favored nation status for one agency over another or trying to create an intermediary genetics czar between some of the agencies and the Secretary. So that probably didn't turn out to be too good of an idea, and none of our ex officios liked that a whole lot.

So we're going to try to figure out some kind of what to get somebody to make sure, you know, the chief of staff or somebody that knows us and can shepherd our stuff through without creating an unnecessary bureaucratic hurdle. So that's the challenge.

I guess I'm reporting to the committee. I am aware of your concerns in this regard and hold myself personally accountable to try to do something to bring us to attention. So we may have to stage maybe a parade in front of HHS saying, "Yea, Genetics," or something, but we'll figure it out.

We also sent the Secretary two letters, one on the incorporation of genetics, genomics, and family history, as Sarah mentioned, into the electronic health information infrastructure and another on direct-to-consumer marketing of genetic tests. Copies of these letters are in your tab 3. In the DTC letter, we recommended that FTC and FDA consider using a joint statement about genetic tests marketed directly to consumers.

Let me just say, as we turn to Dr. Gutman to give us an update, we said in our letter to the Secretary -- and I think we felt good about it -- there was really great collaboration between FDA and FTC on this issue. This was a good example of government working together and working well, and I think it's something that should be noted and applauded, celebrated, modeled.

Steve, where are we on this now?

DR. GUTMAN: Yes. We actually are working on a final work product to produce some consumer information that we think would be very helpful, very clarifying. We hope it would be a strong statement. We are doing that collaboratively with FDA, FTC, and CDC. There has been a lot of recent interest.

As you remember, historically we had actually hoped that one of the agencies might be able to identify a target that might produce the response that would be more than sort of general advice, that might FTC might actually be able to take some action. We actually continued to survey the environment to look for targets where they may have crossed the line and actually violated and deserved some more specific action. I again urge the committee, as I did before, to please keep your eyes and ears open. If you do identify outrageous outliers, I'm certain I would like to know. I suspect Matt would like to know about them.

This is not intended to actually create a solution to a particular problem. It is a general public health notice. It is in final form. Because you are coordinating across three agencies, it probably won't come

out like lightning, but I am certainly hopeful it will come out with reasonable speed.

DR. TUCKSON: Again, Steve, if you would take back to the interagency work group that the committee acknowledged with applause the coordinated efforts there and, within that context, would urge more of the light speed than the reasonable.

DR. GUTMAN: I will try.

DR. TUCKSON: We'd like a real victory on this one. I mean, we've got it now.

On the incorporation of the genetics and family history electronic health record, health information, Sarah, if you would, after this meeting, cause me to call David Brailer. I think we want to really, really make sure that we are personally engaged with David Brailer on this issue. This is a win. I mean, I can feel it. This is low-hanging fruit. We should be able to get this done, and so I want to call him directly.

Today we will continue to develop our reports and recommendations on the large population studies and pharmacogenomics. Tomorrow we will be briefed about the report issued last fall by the National Academy of Sciences on the impact of genomic and proteomic patents and licensing practices on innovation in public health. We'll hear the conclusions of the SACGHS Task Force on Patents and Access about the report and their recommendations for next steps we should take. So those are those two big items on our strategic plan that we will substantively move forward with by the end of this meeting, both large pop and on patents.

We will also be updated on the status of federal genetic nondiscrimination legislation and hear about a new survey of public attitudes that is now available.

Public comments sessions, as always, are scheduled for both days and individuals who would like to provide testimony and have not already signed up should do so at the registration desk.

In order to enhance our currency and ability to stay abreast of developments, the ex officio agencies were asked to provide updates on relevant activities in their agencies and Departments. These updates can be found on tab 4.

Let me just say to the ex officios, we really, really appreciate your involvement on this, and I think it's very good to have those updates to let us know what's going on and to find ways in which we can see more about how we can support and encourage those good activities. We'll hear more about several of these activities during the large population studies, the pharmacogenomics, and patent and access sessions later today and tomorrow.

At the last meeting, you completed a survey about the effectiveness of the committee's activities. The results of that survey are in your table folders, in the folders here. In general, our responses suggest that we think the committee is effective. However, there is room for improvement in some areas, and in particular, some of us would like to see more feedback from HHS about our work and priorities. I know the ex officios have taken this concern to heart and are going to be considering it and other suggestions very carefully. And I mentioned earlier this business about trying to see if we can't find out a little more from how what we do connects to the Secretary's office.

Joseph, thank you for your liaison activity to the HHS Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. You've held your seventh meeting in February, and the highlights of Dr. Telfair's meeting minutes can be found, again, in your table folders. We won't have a chance to go through that today, but Joe, thank you for making that available.

DR. TELFAIR: I just had one minor correction that I need to make to the report. It's on the very last page. It's under G. It's an editing comment. It's because I tried to use the same format. At the top, it should say "Final Presentation or Comments on Tuesday, February 14, 2006," instead of "October 2005." Sorry about that.

DR. TUCKSON: Joe, you are on the case as always. Thank you, sir.

DR. TELFAIR: Okay. You're welcome.

DR. TUCKSON: With that correction noted. Again, nobody needs an extra meeting to go to, but thank you for doing it.

DR. TELFAIR: It's my pleasure. Thanks.

DR. TUCKSON: Thank you. Debra, you are the liaison to the CDC EGAPP Working Group. The working group held their fourth meeting in February. Highlights of that meeting can also be found in your table folders. Any comment?

DR. LEONARD: No. Last time I must have said something I shouldn't have said. So this time Linda provided the update so that I couldn't say anything that I wasn't supposed to say.

But if anybody wants to know how interesting the EGAPP work is, it's really intriguing and they're finally going to be getting to some data and so it's getting very, very exciting.

DR. TUCKSON: Oh, it is. Oh, great. Well, thank you very much.

We've had a change in our membership. Regrettably, Dr. Christopher Hook made the very difficult decision to resign from the committee due to family and professional obligations. I know that Chris was immensely honored to be appointed to this committee and to serve with all of you. He greatly regrets having to step down, and he asked me to extend his heartfelt thanks and warmest regards to each one of you. The Secretary is expected to fill Chris' seat in the very near future.

Two ex officio positions have also changed. Dr. Cristina Beato, Principal Deputy Assistant Secretary of Health, has been appointed to serve as the ex officio for the HHS Office of Public Health and Science. I know Cris really well. She is a terrific colleague and she will serve our committee very well. She couldn't be here today, but thank you very much, Bernard, for sitting in and I appreciate your involvement today. Please tell Cris I said hello.

The Department of Defense will now be represented by Lieutenant Colonel Scott McLean, Chief of Medical Genetics at Lackland Air Force Base in Texas. Dr. McLean could not attend this meeting due to a longstanding commitment, but we look forward to his participation.

Also, we're joined by Linda Johnston-Lloyd, Acting Director of HRSA's Center for Quality. Linda, are you here?

MS. JOHNSTON-LLOYD: I'm right here. Good morning.

DR. TUCKSON: How did you get there? You just snuck in. How are you doing today?

MS. JOHNSTON-LLOYD: I'm fine.

DR. TUCKSON: Great. We're very glad to have you here. You're sitting in for my old friend, Sam Shekar, and again, we're happy to have you involved.

We're also joined by Dr. William Koch. See, I did it right this time, William. He is the Deputy Director of the Chemical Science and Technology Laboratory at NIH Standards and Technology, sitting in for Willie May, our ex officio from the Department of Commerce.

There's also been a transition in SACGHS staff. Our old and good friend -- I guess she's too young to be old because she's still just so young -- Amanda Sarata took another job in December with the American Society for Therapeutic Radiology and Oncology. She was, I mean really, just a terrific staff person to our committee.

But we're real pleased that Amita Mehrotra has now been hired to fill Amanda's slot. Amita earned a masters degree in public health from GW and an undergraduate degree in molecular genetics from Ohio State. So we are very pleased and we're going to work you to death. It will be just terrific. You'll love every minute of it.

Also, Kathi Hanna, a science policy writer, well-known to many of us, has been tapped to help develop our report on the large population study. How are you doing? Good to see you.

I'll now turn to Sarah Carr for her very serious, sober, scary reminders about ethics rules.

MS. CARR: Thank you. As you know, you've been appointed to this committee as special government employees in order to serve. This is a special category of government employees, but you're, nonetheless, required to follow the rules that we must follow. Those rules are outlined in a document called Standards of Ethical Conduct for Employees of the Executive Branch. Each of you received this document when you were appointed.

There are many rules in the document that you are aware of, I know, and I'm just going to highlight two today.

The first one is about conflict of interest, as Reed said. Before every meeting, you provide us with information about your personal, professional, and financial interests, information that we use to determine whether you have any real, potential, or apparent conflicts of interest that could compromise your ability to be objective in giving advice during committee meetings. While we waive conflicts of interest for general matters, because we believe your ability to be objective will not be affected by your interests in such matters, we also rely, to a great degree, on you to be attentive during our meetings to the possibility that an issue could arise that would affect or appear to affect your interest in a specific way.

In addition, we've provided each of you with a list of your financial interests and covered relationships that would pose a conflict if they became a focal point of committee deliberations. And if this happens, we would ask you to recuse yourself.

Let me remind you that you are also prohibited from lobbying. If you lobby in your professional capacity or as a private citizen, it's important for you to keep that activity separate from the activities of this committee. Just keep in mind that we are advisory to the Secretary and not to Congress. Thank you.

DR. TUCKSON: Thank you. With that last comment being who we are advisory to, as we turn now to the large population study -- and I'm getting ready to turn to Huntington in just a moment.

By the way, the latest draft report was e-mailed and FedExed to the full committee on March 20, but also copies are in the table folders. Does everybody have a copy? All right.

Let me just say, as I turn to Hunt, everybody makes this committee a priority for them, and we appreciate it. Joe Telfair just got off a plane from Uganda. So when he goes "pow," it's not that he's not happy. I can't believe he's done it. I'd say that also to introduce Hunt who is on his way in 8 hours to China. So he's here and that's the kind of commitment that people on this committee have, and I just really want to acknowledge the extra effort that people make to get here.

Before Hunt takes us through that, there's one small correction that I just want to handle in the materials. You will see there's an RFA announcement about this from our colleagues at NIH, and in there is a slight sentence that gets at the idea that in the RFA, that they sort of allude to a recommendation that the committee might have made in this regard of sort of supporting this study at the last conversation. A small technicality in that we don't actually recommend these sort of things to the agencies, but to the Secretary.

It means that we will have to work with NIH, and I've talk with the folks with NIH. A slight modification, just a very subtle modification of that language. It's not a real big deal, and I don't want to make it a big deal, but just a matter that we can't quite recommend in that regard. Just a little caution there.

But be that as it may, I think we're all on the same page, that we do want to emphasize how important it is to get the input of the public going forward. So there will be a slight modification of that. But the spirit is the main thing. We're all on the same page in terms of the spirit of what we're trying to achieve here, and so we'll just technically resolve that and be done with it.

With that, Hunt.

DR. WILLARD: Thank you, Reed. Good morning. Actually my being here is not just because I love this committee work, but Sarah is holding my passport and said I couldn't have it back until after this presentation.

(Laughter.)

DR. WILLARD: We actually have between now and lunchtime to go over not only the deliberations of the Large Population Studies Task Force, but the draft report which you have, in principle, seen and

memorized, and to come up with a list of issues that we as a committee feel are important to the charge that was presented to us, and then identify some of the approaches that would be helpful in going forward. Those are the parts of the report that are left blank awaiting committee input today, and we'll need to be fairly deliberate to work through that between now and lunchtime.

So I will zip through my formal presentation as quickly as I can to give you some background of the task force's work to tee up many of the issues that the task force identified as a draft set of issues that the full committee can take on, and then we'll get into a general discussion.

So just as a reminder to those who actually were on the task force and also those who were not, this was the group that convened a number of times by telephone to go through many of the issues and to frame the report that you have in front of you.

The issue, just to remind everyone, not so much what the purpose of the large population study would be and then the resource that that study or studies would represent at the end of the day, was really the goals of those studies that has framed the task force's work and guided the shape of the document that you have in front of you.

What I want to do, both in my formal presentation and then to tee up our discussion session, is give you a bit of background and an update on some relevant events that are described in the task force draft report, focus most of our discussion on the various issues and potential approaches. And the charge to us today before lunch is to try to come up with a committee's view of what relevant approaches might be and potential recommendations that we can then shape going forward before we make those recommendations to the Secretary.

A little bit of background, to remind people where we've been. So we were requested by the NIH, now almost, heavens, three years ago, to begin to weigh in on the value of a large population study. This coincided with an important paper that Francis Collins wrote publicly making the case for such a study and the resource that it would represent. During our priority-setting process, as we heard just a few moments ago, this was categorized as one of the issues that required in-depth study, and then our task force was developed in October of '04 in order to begin work on this point.

A year ago, we had a full-day session presenting both different scientific approaches that have been taken or proposed to explore the kinds of relationships that a large population study would explore between genetic variation, the environment, and common disease, and as well, identified many of the scientific, social, ethical, and legal issues around such studies that we as a committee would need to weigh in on.

At last summer's meeting, we agreed to begin to develop a report to the Secretary that would identify those key policy issues, outline approaches that could be used, and then ultimately make recommendations about the types of mechanisms that would work best to address the issues that we identified.

Last fall, we had another day-long session with a number of in-depth presentations from scientists, ethicists, and from some public engagement experts to give us some insight into not only the key policy issues that exist around this issue, but also how to address them, and especially public engagement mechanisms and best practices in order to inform us of, again, the range of possible mechanisms that we can discuss later today.

The outcome of that meeting led to an identification of a number of those policy issues, gave us enough information to move forward to a drafting of the report, and importantly, as an overarching issue, reaffirmed this notion that the public must be involved at all stages of the development planning and the conduct of any kind of a study that would go forward. And it's that point which has guided much of our thinking on the task force and much of the drafting of the report that you have in front of you.

At the October '05 meeting, essentially a straw vote around the table was that despite the challenges of the study, there was clear, initial enthusiasm for the study concept because of its great potential. This was, I think, uniformly held, although the degree of enthusiasm or the degree of level and number of caveats that individual members of the committee expressed was quite variable I suspect. So that was despite the challenges.

But in addition, because of the challenges, we also recognized the need for in-depth analysis of the issues and the kinds of approaches that we need to be taking before any final decision might be made to go forward or not go forward with such a study in the United States.

So we aimed to develop at least the framework of a draft report in time for this meeting and that was put forward with the terrific assistance, first, of Amanda Sarata and then, in heroic fashion, Kathi Hanna, who stepped in to help us draft the report that you have in front of you.

Also at the October meeting, we were asked by the NIH for a sense of the committee -- and this is the point that Reed just alluded to -- on whether it should proceed with public engagement efforts. And as Reed just said, although in our advisory role, we can only recommend to the Secretary -- and that's the kind of recommendations that we'll discuss today -- but, nonetheless, we indicated that given the obvious importance to us of public engagement, we didn't wish to inhibit the NIH in moving forward, which I think was classic language that came from our chairman. And as you just heard, an RFA was, in fact, put out by NHGRI in order to take the first steps in that direction.

So there have been a number of other developments which are described in your booklets, and they'll be alluded to, I'm sure, during the discussion, and we can discuss them at greater or lesser extents, as people wish.

First was the Gene and Environment Initiative, GEI, announced by Secretary Leavitt as a key effort of HHS and the NIH.

The Genetic Association Information Network, another related study, as a partnership between the NIH and the private sector.

Further progress on the National Children's Study.

The RFA from NHGRI that I just alluded to.

And then the announcement by the VA that it was going to form an advisory committee on genomic medicine to guide its efforts for the program that it is hoping to mount in this direction.

So there's plenty of activity that's going on around us and that our work can, hopefully, inform and we can, again, reflect off of these to guide some of our deliberations this morning.

So we, being the task force, were charged at that October meeting to draft a report. There were three steps to this charge.

First, to delineate policy issues and the questions that policymakers would need to address. And the first attempt at that is contained in the draft report in front of you.

Two, to explore the ways in which these questions might be addressed, including any variety of smaller, intermediate research studies, pilot projects, or policy analysis efforts that will be needed, and that's very definitely what we're to talk about today.

And then thirdly, to determine in the committee's opinion which approaches are optimal and, therefore, would form the basis for recommendations to the Secretary, and that's also on the docket for discussion today.

So the scientific background of the report, which you've all read, is shown here, describing briefly the kinds of methods that would be used and are being used to identify the genetic basis of disease, especially common diseases; providing some background, which you've also heard several times in the life of this committee at these meetings, of various biobanks around the world in large population studies around the world; and then an overview of a hypothetical large population cohort study mounted in this country, as outlined initially in that paper by Francis Collins and subsequently addressed also by an expert task force or working group, whatever the official name was, that NHGRI pulled together to examine some of the scientific issues.

So there are really six key points that the task force identified, and that provides the framework for the report that you have in front of you. There's an overarching issue, which is this need for public engagement, and that we addressed by itself in the draft report, but it also provides relevant points underneath each of the other five issues which have around them a series of questions and issues that the committee will have to finalize today, those five policy areas being research policy considerations, research logistics, regulatory and ethical considerations, public health implications, and then finally, social implications. And in all of those, to repeat, we would anticipate the need for public engagement in order to best inform those as we go forward.

So, first, why public engagement matters. What this is is a screen shot of a brief editorial that came out in Nature in the March 16th issue with the headline that says, "Huge Biobank Project Launches Despite Critics."

The notion there was that the U.K. Biobank is actually getting off the ground and beginning to collect samples from their ultimately hoped-for half a million participants. But there are still critics some many years after they have engaged in a series of public engagement efforts. We heard from representatives of the U.K. Biobank at at least one, if not two, of our meetings. So they've actually provided a model for how we might go forward, accepting and acknowledging the sort of cultural differences both in science and the society at large between the U.K. and the United States.

Nonetheless, having done that in a diligent and open fashion for several years, they still have a large number of critics who are saying that the project isn't ready or shouldn't be taken up or who are concerned about the kinds of information that would come from it. And one of the issues is that -- and there's a quote that is shown on that -- the "complaints stem in part from a misunderstanding of the scheme." So

even several years down the line with that study, and the cohort study and the resources it would represent, being outlined and aired in public again and again and again, there still is an acknowledgement that there's a misunderstanding of what they're trying to do and what the purpose of the Biobank would be as they set out to do it.

So I think this provides to us a bit of realism of the challenge in front of us of exactly why a public engagement in this public engagement in this country will matter as we go forward.

So here, just highlighting some of the points that are also made in the document, why public engagement matters. It's expensive. The public always pay attention when there are expensive projects of this magnitude. The scale of the study dealing with a half million to a million Americans is enormous and enough to get public attention, and those are not only people who potentially might want to be enrolled but also people who in their viewpoint especially would be exposed to the potential risks, as well as the potential benefits, of course, of the study as it goes forward.

It's a long study, which means it will capture people's attention and immediate results will not be forthcoming. By definition, this is going to take substantial time before potential benefits will accrue.

And then because of the potential significance and social implications of the large population study, public engagement will be necessary again at every step.

So one of the key questions that the task force identified in the draft report is at what level does one engage the public. Is it at a go/no go decision point, whenever that decision point might be? Is it at the level of the study design and planning? Is it at the point at which the study actually initiates in which you try to bring the public along at that point, or is it throughout all phases of the study from the very beginning, all the way through to the very end? Those are questions that the committee can choose to endorse or debate, and hopefully, we'll get to that later this morning.

Another question is, what do we actually mean by the public? Engaging the public means different things to different people. Are we talking about the lay public, the individuals whose samples might be or who might actually participate in this large study? Are we dealing with the scientific public? Are we dealing with our elected officials both at the federal, state, and local levels who would be dealing with this at some level, or again, all of the above? And perhaps the mechanisms and the approaches that one might take to engage any of these three groups might, in fact, be substantially different.

When does one engage the public? Right away? Later, when a decision about the study is made, again either go or no go? Or is it after study design and planning have been completed so that there is actually the details of a study laid out in front of the public? What questions might be the public be asked for their input, or is it all matters that one might ask for their input? And again, which subgroups of the public need to be engaged?

So those are the overarching issues that I think we need to keep in mind in trying to guide or shepherd some of the discussion for the rest of this morning. I'll continually come back to this point I think.

So then there are five key policy topics, and I've arranged my slides here in this manner, identifying each of those and going through the various considerations and the questions that the task force identified, which the committee, again, is invited to either agree, disagree, add, or subtract as we go forward this

morning.

The research policy considerations that are relevant are questions like what is the need for such a study. What is its value and cost? What would the effects of funding this program be on other areas of research priority in this country, and can existing studies either in this country or elsewhere achieve many or all of the same goals? These are not scientific questions, but these are science policy questions that the task force felt were important for advising the Secretary.

Additional questions. Should there be collaboration with other countries, as I just alluded to? Which agencies in HHS should be involved? Which agencies should take the lead in such a project if one is going to be mounted? What should be the role of the private sector? And here I think this is where the GAIN project, which has been announced as a partnership with the private sector, is both exciting and very relevant to our deliberations this morning. And what intellectual property policies might govern the study as a matter of research policy?

And lastly, given that the long-term cost required to mount such a study would be significant, if not unprecedented -- and there clearly is a lot of uncertainty about the ultimate costs of such a study -- would it be possible to sustain support at all the levels, public, scientific, and elected officials, for such an investment over such a long period of time?

So those are the questions the task force identified, and there are a number of issues relevant to those research policy considerations that are outlined in the report, and the report is organized exactly in this manner to remind you of what, hopefully, you've already read through.

And continuing, so not only the need for and the potential benefits of the project, but its costs and effects on other areas of science priorities in this country, the current capacity to conduct such interdisciplinary science, the potential need for various partnerships, and intellectual property concerns and access. And each of those issues is flagged in the report.

Policy topic number two related less so to the policy issues and more so to the logistics of such a study. How will representativeness be defined and achieved in terms of who are the 500,000 to 1 million potential participants.

Given that the study's benefits to individual participants may be only indirect, would it be difficult to recruit a broad range of study participants? And the experience in other countries is probably relevant in this regard.

What are the ramifications of using racial or ethnic categories for codifying different participants? That's an issue which I think the task force felt quite strongly that there were a number of issues there that would have to be examined before going forward.

And then will the underinsured or underserved be part of the study, and if so, how does one ensure that they're recruited in sufficient numbers?

Under research logistics again, how will the non-genetic study variables be defined and studied in the realm of the large umbrella called environment?

Given that this is going to need to be decentralized to several different sites around the country, if not many different sites around the country, would the lack of uniform methods that define our health care system in this country make a study of this scale either difficult or impossible to implement?

And will new technologies be required especially to collect environmental data? Within the NIH NIEHS is substantially ahead on this issue in defining exactly the kinds of new data that will need to be collected and the new technology developments that will have to be in place.

The issues that are flagged in the report around research logistics involve enrollment criteria and recruitment of racially or ethnically defined groups measuring various differences in the population across many different sites, coordination across multiple institutions and health care systems in this country. The committee again will have to weigh in on those particular issues.

You'll notice, just if I can take pause here, what I'm outlining are the questions and the issues. The task force has not outlined, although we have some ideas and some thoughts on this, the various approaches that would be used or could be used in order to address those questions and issues. Again, that's what the full committee needs to be thinking through in order to guide our discussions later.

Key policy topic three on regulatory and ethical considerations. The questions here of regulatory requirements and how they might be met, how informed consent would be carried out and obtained, and whether there are unique considerations for a long-term study of this magnitude. Would the study provide health care to uninsured participants, and if so, how would that work? And are there special protections for children or adolescents who might be enrolled in such a study?

Who will have access to study data and under what circumstances and how? Does that, therefore, require special arrangements to enable the participants to have some measure of control over how their individual samples or the data that would be obtained would be used and by whom?

And would the study be able to accommodate participants' expectations regarding the confidentiality of their data? This goes, obviously, to the much larger issue of privacy of genetic but even also environmental data, which we've tackled on several occasions previously.

Will additional privacy protections be necessary and for how long, and how would the research data and samples be stored?

And would the study results be returned to participants and under what set of criteria?

Again, many of these questions are addressed in many different settings, many different projects, large and small, but because of the large-scale nature of this particular project, the task force felt that it heightens the awareness of these issues and therefore their importance.

What Federal laws and regulations would be needed to be considered in deciding whether to return or not results to participants and their family members, and then how does one deal with the issue of family members who may not themselves be participating in the study, but who clearly would be interested in the information because it would be relevant to their own health situation?

The issues flagged as a result of those kinds of questions dealing with IRB review, informed consent,

whether, in fact, it is possible to have informed consent, given the lack of public understanding about a study of this nature and the level of prospective thought that needs to be in place.

Issues related to providing care and what the report refers to as the therapeutic misconception about what can or cannot be done when the data are available, privacy and confidentiality issues, control of samples and data issues, and then the larger issue of returning research results or not.

Topic number four, more in the public health realm and the implications of that. Will the statistical genetic associations be robust enough to lead to new therapeutic or preventive strategies?

Will such a study widen the gap between what can be diagnosed and what can be done about it, which is a standing problem in many such studies but may be particularly acute in a study that's this large and this publicly discussed?

And will all the data from the broad population be applicable to individual communities and groups who are defined by a variety of different cultural, genetic, and ethnic means?

How will the study results be implemented by regulatory health and safety agencies at different levels around the country, given the complexity of population risk assessments and the balance between population risk and individual risk assessments?

And do the regulatory agencies, public health departments, and health care providers have sufficient resources in order to translate the knowledge that such a study will generate? This, obviously, is a longer-term issue, but there's a need for those health care providers and regulatory agencies to be ready to act on the data as they become available.

Last on the list, but not last in importance, of course, the notion of the social implications relevant to a large population study of this magnitude. Could such a study create or change the way that we currently think about health disparities? Will the findings exacerbate existing vulnerabilities, such as age, race, and disability? And if the study leads to the identification of new vulnerable populations, will there be sufficient public health or social resources available to respond to such new vulnerabilities?

If the study generates clinically useful information, will it benefit only those who currently have access to the health care system and how does one ensure that, in fact, all citizens in this country would benefit from those findings?

Can or how would the study results be realized in what is currently a significantly decentralized and fragmented health care system? This is clearly one of the differences between a U.S. study of this type and similar studies mounted in other countries that have different health care systems.

And would the findings from such a study exacerbate racial discrimination or other types of discrimination and group stigmatization?

What are the views of minority communities about the study's implications?

Will the study pose or increase risks of genetic discrimination?

And will the study findings lead to very reductionist explanations of the role of genetics in disease, which has been a challenge for the genetics community for some time?

The issues that are flagged in the report to address those questions relate to elucidating and/or exacerbating health disparities, the risks of genetic determinism, developing reasonable social and policy responses to anticipated research findings. And all of those questions fit largely under those three particular bullet points.

So our goal today is to review and discuss the policy issues that I just ran through, and hopefully that you have read at leisure in your looking at the report, go through those for completeness and relevance and less so wording. This is not a wordsmithing session. We're nowhere at that point, but we do want to have a fairly complete list of the issues that the committee at large feels are relevant to the policy issues that I've just outlined, and determine whether they should be prioritized. In what I just spelled out, there was no effort at prioritization. It may be that some of the issues are considered to be a substantially higher priority than others, and if so, do we want to prioritize them within the report?

And then most importantly, we wanted to discuss approaches today for addressing those policy issues and developing additional options, which would lead us then to a series of mechanisms that we might recommend to the Secretary which was, in particular, the charge passed down to us by NIH Director Zerhouni.

So in kicking this off, I want to come back to the larger broad issue of public engagement mechanisms, mostly to point out exactly how large and complex these issues are, at least in the eyes of the task force and use that as a point of departure for moving into a broader discussion of all of the issues that we've identified.

So when one thinks about public engagement mechanisms, there are a series of different mechanisms that one might contemplate, depending on which issues the public is being asked to address. So if they're being engaged around the actual initial conceptual question of should there be a large population study of this type, then as we heard in some of the presentations last meeting, there is a range of different approaches from surveys carried out nationally or locally, state referendums, trying to work with Congress directly to look for their support or funding in their role as the elected officials representing the public, town meetings around the country, focus groups, and on-line collaborations in order to provide Web-based materials for the public. And to greater or lesser extents, each and all of these have been used in other countries where the mechanism is relevant to obtain support for the programs that have already been outlined in those countries.

If, at a different level, the question is to engage the public around operational questions concerning design, planning, conduct, follow-up, and reporting of the issue -- and this isn't to argue that the public is going to tell the scientists what to do, but it is to say that the public may have a role in order to, at some level of sort of a 5,000-foot view, comment on the kinds of questions and aspects of the design of the project that they might find relevant, again possibly town meetings, focus groups, or Web-based collaborations.

A group of us took an initial stab at some of the issues just to frame again how complicated and how complex issues of public consultation may be. From the original conceptualization of such a study, outlined at least first publicly in the paper that Francis Collins wrote that I've already alluded to, the NIH

pulled together a design considerations work group in 2005, and we entered the fray also in 2005, but now in 2006.

Around the issue of public consultation, there's actually consultation at a number of different levels and with different people. We've identified all of this, in principle, would happen before one would move into the pilot stage, whatever the pilot stage for the ultimate project is, whether it's this detail or some other detail, and then kicking off the actual project, the kicking-off stage being where the U.K. Biobank is now, having started back here at least three, if not four, years ago and maybe even longer. Francis, I'm looking to you. For the U.K. Biobank four years ago. So this for the Biobank was a four-year process before getting to kick-off.

But to make it a little more complicated, at the consultation stage there's actually a large number of different groups that can be analyzed in public consultation. There are issues around protocol development that would have to be tackled. There are very substantial issues around education and training not just of the public, meaning the research participants, but also the physicians and scientists who would be involved and policy experts at different levels around the country that would be interfacing with this project as it would go forward, and then very substantial issues around database development, privacy, who would have access to that database, what structure would it be, et cetera.

Ideally this would be an iterative loop among all of those, as I've attempted to outline here, because in the general public at large, one might contemplate surveys or focus groups, town meetings, as we mentioned, and a broad-based educational campaign, perhaps similar but inevitably on a larger scale than what happened in the U.K.

There are also disease advocacy groups around. I've listed three here, but there's a whole host of advocacy groups around the major common diseases that would likely be encountered during the lifetime of such a study. And these are groups which are important not only because they've given substantial thought to the specific issues that they would be interested in as representatives of the public around their particular disease, but also because having them on board, if there's a decision to go forward, will greatly assist issues of general public engagement through arrows that are not on this slide but which would tie these two together.

And then public consultation of the scientific and professional organizations both to address scientific merit, which is not our particular remit, but might be a remit of other groups, but also at the level of the National Academies or the Institute of Medicine and other groups involved that have both experience and would be needed to assist on issues of either recruitment or data collection or study design.

So there are really three very different levels of public consultation which would have to, at some level, go on separately but then somehow interdigitate with each other in order to develop some kind of matrix of public engagement information that would be relevant to then feeding back on a project. This wouldn't go on simply as an ancillary activity, hopefully to "talk the public into this" as a good idea, but that this actually would feed back on the larger design where one would need to be prepared to act on the feedback and, if necessary, revise the study goals or design and go back in an iterative manner through multiple rounds of consultation, all of which might ultimately then precede a go/no go decision either at the level of HHS or the Congress or the various groups that would be called to do that.

So I outlined that simply to illustrate the magnitude of the challenge that I think our committee has before

us not to have the final word on any of these issues, but to identify what the issues are, raise the questions, and really anticipate what we think some of the most successful mechanisms might be to deal both with the public consultation issues, but also the five key policy issues that I outlined previously.

So I think at this point, what I would like to do is open this up to initial discussion and response and information-gathering among members of the committee, including the ex officios. Then once everyone has had a chance to weigh in on what the task force has done, move into a much more deliberate analysis going through each of the key policy areas that we identified in order to take a look at the questions, take a look at the issues, decide what we want to do with those, and then go to potential approaches and mechanisms. That will then help the task force after this meeting as we go back to continue our work and help Kathi with continuing to draft the report, ultimately getting to a point at several meetings from now where we would come back to finalize the report from the full committee.

So, Mr. Chairman, I will stop at that point.

DR. TUCKSON: First of all, a terrific report.

Could you, again, just level-set for us all again in your mind, or if anybody can, what the actual process time line is for everything? At the end of the day, if this is going to happen, how much time do we have in our recommendations in your committee to be able to give input before it's not relevant anymore to what's actually happening? Is this process going to go on for another couple of years?

DR. WILLARD: I can answer it from the standpoint of our committee and the task force work. I think we'd have to ask Francis or others to weigh in on exactly the timeliness of this. If we're going to go to all of this trouble and we're going to make recommendations, we certainly want the recommendations to be useful to the Secretary and not to come in post facto where they would be of limited or no use.

I think, depending on how far we get today with framing the issues and the approaches and mechanisms, we could come back to this full committee with probably a penultimate draft report at the next meeting. I'm looking at Sarah for her nodding or not nodding. But ultimately for this committee to then approve a set of potential recommendations to transmit to the Secretary, that's realistically at least two meetings down the line I would think.

MS. CARR: The other thing that we had talked about was taking our draft report and opening it up for public comment. It's what we did with the coverage report. So Kathi and I had a back-and-forth. A lot depends on the deliberations of the committee this morning and how much input you give and how far we can take the report, I think, after this meeting.

If we feel like we can put it to bed in draft form after this meeting -- and Kathi has indicated that she might be able to work with that and get a draft done in a couple weeks -- we can then take it out for public comment and actually have a report back in June that might, if there's time, reflect input from the public as well, or at least allow you to consider the public comment in relation to the draft that went out for public comment. So I think that might actually be doable, to see a final draft report in June.

DR. WILLARD: But that would mean the final report and recommendations would be an action we would take in October? Is that correct?

MS. CARR: Well, I mean, conceivably. I guess a lot depends on how things go this morning. But conceivably you could be looking at the final draft in June. It would be very heroic, I must say. And it would only, I think, be possible to allow for a 30-day public comment period then too. If you wanted to give more time and actually get it out there in a wider way, it might require more time than that.

DR. TUCKSON: Let me ask Francis to comment, and also in your comment, Francis, could you, if it's relevant, connect it to the budget struggles that are going on? Hopefully, by the way, I think you all finally got some money back or are about to get some money back to have a real NIH again.

DR. COLLINS: Do you want to see me cry this morning?

(Laughter.)

DR. COLLINS: So thanks for the opportunity to comment. Again, thanks to this task force that has put together a very thoughtful report, which I think outlines, in a very effective way, a whole series of issues that need to be addressed if such a national program, which really would be quite a landmark, quite a historic undertaking, were to get underway and something one would only want to do with a great deal of confidence that the important issues had been addressed.

Let me just say a couple of words about timing issues, but maybe first something about this RFA that has already been issued to try to collect public input about the feasibility and advisability of conducting a large-scale cohort study in the United States.

You have in your briefing books under tab 5 an excerpt from that RFA. It's not the whole thing, but the majority of the critical points are represented there.

Again, I know we're being careful here to say the Secretary's advisory committee did not ask NIH to do this. I did go back and review the minutes of exactly who said what at the end of the last meeting of SACGHS, and if I can quote from our chairman of this task force, Dr. Willard said, "I would think you have the sense of the committee that this is a high-priority item that no one knows how to tackle, and any efforts to learn more about how to tackle it would be welcomed." Okay. So we take that as not urging us to do this, but the notion that this would be useful information.

With that in mind, a lot of work went into then designing this RFA, particularly on the part of Jean McEwen and Terry Manolio. As you saw, it has now been issued. The letter of intent is due April 10. The applications are due May 10. They will get reviewed this summer. It will go to counsel in September, and we hope to have this funded during the current fiscal year, that is, by the end of September.

This is an RFA for a specialized center to conduct a variety of different kinds of approaches to seek public input about such a study, and that would be expected to include surveys, focus groups, and public meetings. We are hoping there will be lots of applications to this from the centers out there that are capable of doing such things. I would think this would be pretty interesting work for the appropriate applicants to plunge in on. And we have set aside \$1.55 million over the course of two years to fund this effort. So it's a two-year effort.

As far as the timing question, we would expect the results of this to be reported out in September of 2008.

So, again, that's a two-year time table from the start point, and I think probably to do this well, you can't compress it much more than that when you consider the planning that has to go into it and then the conduct of what we expect will be public consultation all over the country in various settings with different populations, different backgrounds, different socioeconomic status, access to health care, and so on.

DR. TUCKSON: Francis?

DR. COLLINS: Yes.

DR. TUCKSON: You put a lot there and it was terrific. Let me just make sure I've completely got it.

The first thing you said, which is important to hear, is that money is already put aside.

DR. COLLINS: Yes.

DR. TUCKSON: So there is something that will happen and it does not depend upon any further funding cycles to get it started.

DR. COLLINS: No.

DR. TUCKSON: So that's key. So that's real.

DR. COLLINS: That's real. That's from NHGRI's budget.

DR. TUCKSON: So, number two is that the RFA concludes on which date again?

DR. COLLINS: The applications are due May 10, review this summer, funding by the end of September of 2006.

DR. TUCKSON: September of this year, funding.

DR. COLLINS: Yes.

DR. TUCKSON: So, in other words, the train will leave the station. At the very beginning, the first leaving the station at any level in this project happens in September of '06. Something starts happening. Something will happen that the American people will want to be involved with this starting '06. Not theoretical anymore. It's moving.

DR. COLLINS: But, again, this is an opportunity to collect public input. It is in no way a commitment to actually undertake such a study, both because the public may decide they don't think is a good idea or we may never be able to identify the funding to conduct such a study.

DR. TUCKSON: Then the other thing would be is in terms of -- and I see some other committee members -- but, Francis, as you look at the questions the committee is answering, from your analysis of them, how do you view the overlap between what this September 6th initiative will do and its collection of information -- what is the overlap between the issues we have laid out and what this will do?

DR. COLLINS: I think it's pretty significant. I'll read you in a moment the bullets that we are specifically asking grantee applicants to cover in their proposals.

But let me say, though, right up front, this is not intended to be the full extent of a public consultation for a project of this sort. This is very much a first step. If the project, two years from now, appears to be gathering momentum, public consultation, as was just pointed out by Hunt, will have to be integrated into every step along the way, and this would only be sort of an initial snapshot of public opinions and public concerns.

Now, let me say the things that are being asked to be surveyed, as funded by this RFA, include the acceptability of the goals of the initiative for the U.S. as a whole; concerns regarding uses of data for individuals, communities, and the public at large; expectations about privacy protection; acceptability of open-ended consent, which will probably be necessary for a study of this sort; acceptability of a central IRB; optimal approaches to recruitment, particularly regarding identifying and contacting family members; the need for tailoring to individuals or communities with special needs; expectations about return of information to individuals, communities, and the public at large; the need for an ongoing dialogue with participants regarding study goals and processes; the advisability of including or excluding children; and intellectual property concerns. That's not intended to be an exhaustive list but that is an exemplary list of the kinds of things we hope this public consultation will include.

DR. TUCKSON: Hunt, you're now back in because I actually wound up asking a question and you'll lead us through.

I just want to make sure that we're completely clear so everybody is on the same page here and we all understand. We have a set of things that we think that our committee thinks ought to be looked at. This is an RFA to look at certain things. So we have to see how the RFA, which is funded, which is going to happen, goes forward. It is not theoretical. We can't influence the RFA. It is already on the street. It is already there. So they are going to move forward. So our questions really have to deal with now the reality of that and then what things we see doing in the context of that.

So with that, Hunt, take it away.

DR. WILLARD: Thank you.

What I would say, though, is -- and then Francis said this as well -- this is simply a pilot project to do first-round public engagement issues. So that doesn't mean that our advice wouldn't be useful for a subsequent round of a much more extensive series of public engagement efforts.

DR. COLLINS: And can I say your advice would be useful in this round as well because this is a U01. This is the kind of a grant that involves extensive staff interaction with the granting agency in terms of the details of how the consultation is conducted. So if there are areas that this group is particularly concerned about that need to be emphasized, we're listening to that, and that's a great opportunity then to try to sculpt and craft this particular approach so that we are not missing the boat.

DR. TUCKSON: One other thing I should have asked before I turn it back to Hunt. This is actually asking you not to read the tea leaves of the future but more of your strategic intent.

There is a pretty strong commitment on the part of NIH, and HHS at some levels, to try to do this study. Obviously, you guys are pretty revved up about this. Is this public comment part meant to be part of a future go/no go decision from this RFA, or is it meant to help advise on how to do the study well?

DR. COLLINS: I think the decision about whether, in the United States, this study is ever going to happen is very much up for grabs. I think the scientific arguments for the value of the information are quite compelling, which is why many of us are, as you say, revved up about this. Certainly the group that we convened that worked on the details of a scientific plan and the study design came away from that experience, after more than 12 months of very hard work, unanimously convinced that this is the kind of study that would provide critical information about genetic and environmental contributions to disease that we otherwise will not have a few years down the road and which we'll probably regret not having.

At the same time, everybody recognizes that this is the kind of study which has enormous consequences, both in terms of public acceptance and in terms of budgetary implications at a time where budgets are under severe constraint.

So there is no certainty at all about whether all the discussion we're having, even if it becomes totally convincing scientifically and in terms of public benefit, will lead to a yes decision to go forward. There are no funds in the FY '07 President's budget to support a large-scale United States prospective cohort study. We're delighted about this initiative called GEI, the Genes and Environment Initiative, but it is not about a prospective cohort study. It is about case-control studies, also a very exciting opportunity and one that we welcome, but it in no way implies a commitment to going forward with this kind of prospective effort.

You've also heard, no doubt, that there are no funds in the FY '07 President's budget to support the National Children's Study, another prospective cohort study, which has had five years or now six years of planning, and which, at the present time, still is very much in limbo as far as the possibility of long-term funding support, again a rather expensive undertaking for which, frankly, I think the stomach is just not quite there yet in terms of the ability to support these things.

So I think our best task -- again, I appreciate the committee going forward with this -- is to continue to explore public receptivity and scientific value of this while waiting to see whether the funding climate can change in some way, recognizing that it may not.

Certainly in terms of your specific question, Reed, about the budget cycle, just a quick tutorial on how that works. The budget for FY '08 will already begin to get constructed by this summer. By June or July, those discussions will begin. That's the kind of lead time there is. So if one wanted to have an influence on that in some way, having a report out of this committee by June would be useful. Otherwise, it gets a little late to influence FY '08 and then you might slip back to FY '09. Those are just the realities of how this very complicated process plays out.

DR. TUCKSON: Well, that's what I was looking for, is that sort of sense. So, Hunt, as you take it over, I think that what is in front of us -- again, I appreciate your continuing to keep this clear for us -- is if this committee feels that this is an important activity, really important in terms of the study itself, and we feel that it be conducted with certain public input considerations, then we're going to need, I think to be relevant to this, to be prepared to have something to say in June to the Secretary about this matter. And I think that come heck or high water, regardless of how sophisticated that is, we need to be communicating

some sort of statement in June if we want to be relevant to the course of events. So I just suggest that there, and I turn it over to you.

DR. TELFAIR: I actually have two questions, but I'll ask one and then I'll come back after the rotation for another one. Is that okay, Hunt? Okay.

The first question I have is that given everything that you said -- this is to you, Dr. Collins -- everything that has been put out in terms of this initiative, I was wondering, because it's a logistical issue and it's pretty important to making some decision about this, is the review committee for the proposal an internal or an external committee review on this? I'm not as familiar with this type of granting process. So I just was curious on that because where the committee comes from, as you well know, is going to dictate what happens next.

DR. COLLINS: So that will be an external review committee. It will be a special review committee put together to review this particular RFA. It will be a review conducted by the Genome Institute's review staff, who I think are pretty well connected with the expertise in the field for this kind of a proposal.

DR. TELFAIR: Thank you.

DR. WILLARD: To follow up on that, Francis, can you say a word about the thought process that went behind making this a U01 instead of an R mechanism?

DR. COLLINS: We had various debates about this, and some people are even advocating it should just be a contract as opposed to a grant. We've actually had very good success in circumstances like this with the U mechanism which allows for a lot more involvement of staff in the ongoing conduct of a program of this sort, as opposed to where you give the money away and then you cross your fingers and hope that, two years later, the work product you were hoping for comes back to you. So while it's not quite as cut and dried as if you have a contract with timetables and deliverables, you still have a lot more ability to be sure that what you get for your \$1.5 million is pretty close to the work product you were hoping for and you don't end up with something that's sort of way off the mark.

I think the consequence of our running this as a U01 is that people like Jean McEwen and Terry Manolio will be tracking very closely how the process is set up and how it's conducted and making sure, all the way along, that we're getting the kind of diverse perspectives that we need and the kind of specific issues addressed and something that will come back that will be useful for all of the decision-making that will follow.

MS. BERRY: I was wondering if in the RFA and/or the task force's deliberations there was any thought to comprehensive, extensive media campaigns to educate the public first, or if not, was that by design? In other words, is it better to have people start with a blank slate? Because I think the general public is probably there. They have no clue about this at all. So is the objective to educate them first and then have the focus groups and surveys to gauge their thoughts after hearing from the media and others? Because most people get their information on health matters really from what they read about or perhaps their doctor. So I just wondered if that was a component or an intended component of this phase or whether, purposely, it's to be excluded until this RFA proceeds.

DR. COLLINS: Well, we're always going to be interested to see what creative ideas the applicants come

up with.

I think a large media campaign might actually be quite misleading at the present time since we don't really know if we're ever going to do this study. So to try to educate people about it without that decision having been made, we may end up having a response to that that's something we don't quite know how to deal with.

I think the goal here is to do the education with the groups whose opinions are then being sought rather than trying to do education broadly across the general population because we're not going to hear from everybody in the population. We might confuse the people who weren't part of the study.

DR. LICINIO: I have a question for you, Francis, because this Genes and Environment Initiative that's already out there sounds very compelling. You have the genes, we have the environment, so we can figure everything out. But I'm actually just reading here straight from the announcement. It says that there will be two components, the genetic and a technology development program to devise new ways of monitoring personal environmental exposures that interact with genetic variations and result in human disease.

So the way it sounded is the environment is just like toxins or things you can measure. All the psychosocial components of the environment, which are crucial like poverty, death, separation, trauma, abuse, whatever, none of these can measure the device. So when you talk about your large-scale study, do you think about the environment like toxins that you can measure with a machine or the environment at large?

DR. COLLINS: That's a great question. In fact, this GEI, Genes and Environment Initiative, having just been announced in early February, is something which NIH is now trying to figure out how will we actually conduct this research, assuming that Congress goes along with the proposal, which they may or may not. This is, at the moment, a proposal in the President's budget and we won't know for many months whether it's actually going to happen.

I'm actually very pleased with the way in which this has been put forward as a genes and environment interaction focus. And I think it does have some relevance to what we're talking about this morning, so I appreciate your bringing this up. Certainly the environment is much more than toxin exposure, and I think there's a good deal of sensitivity to that as we try to design how this \$40 million a year effort would go forward, how do you try to push that agenda from sort of superficial analyses of measures of environmental exposure to things like stress and other kinds of socioeconomic factors.

But there also is a great need here, I think, to push the agenda as far as developing better technologies for specific environmental exposures, which would be very relevant to a large-scale population study. If we were starting such a study today, we'd want to be able to integrate into that every kind of sophisticated measure of environmental exposures, body burden, body reaction to such exposures. How can you assess the biological consequence of this kind of an exposure to the individual? And also, diet and physical activity, things that we currently measure rather poorly frankly, could be much more accurately measured with some of the new technologies that are coming along and just need, I think, a big push to get them to the point where they could be applicable in a very large study. And that is a specific goal of part of GEI.

So while GEI is not in any way intended to imply a commitment to go forward with a large-scale

prospective cohort study in the U.S., some of the tools that come out of it clearly could be quite valuable for that purpose.

But I take your point, that when we talk about environment, we really need to talk about environment with a capital E and not think small.

DR. WINN-DEEN: I wanted to ask a question that comes with my background in GMP validation. Have you outlined any kind of an endpoint acceptance that if you achieve public acceptance at 80 percent or better, then you would proceed, you know, just some metrics that you would use to measure whether you should proceed to the next step on the basis of this public consultation? Or is this strictly just information-gathering without any real hard pre-ordained ways to analyze the data at the end?

DR. COLLINS: At the moment, I would not say that we have defined some kind of threshold above which positive responses have to rise in order to make this an acceptable project. Again, it's not as if you're asking one question of the people you're consulting with. You're asking them many different types of questions and the receptivity may be quite variable depending on the question and the group you're asking. Would it be acceptable to go forward if 98 percent of white people said fine and 15 percent of minority populations said fine? That would make you pretty uneasy, wouldn't it?

So I'm not sure exactly how we could predetermine those outputs. Again, we're depending on the applicants, really, to use their creativity to come up with the specifics of how to do this, so I'm not sure exactly how we would know now what the answer would have to be in order for us to be comforted.

DR. WINN-DEEN: Do you anticipate that there will be some way to measure whether you should go ahead based on whatever you get back? I understand what you're saying, that there are lots of questions. I guess my concern is that if you do a two-year consultation and you don't know how you're going to respond to the information you get back, it's an interesting exercise. It adds to some body of knowledge on people's sort of social reaction to various things put in front of them, but it doesn't really lead us to a positive way to say we should take the next step forward.

DR. COLLINS: I guess, Emily, I'm thinking of this more as an opportunity to find out where are the areas of greatest concern, which you could then adjust your study design to take account of and try to diminish those concerns as much as possible. I think the evidence we have from a much more informal, less structured efforts would suggest that there's a lot of the public that's going to be fairly positive about this as long as certain provisos are included, certain protections are included. I don't think we're going to find that there's very strong objections across the board to the concept, but I think there will be issues about the details that will come out of this kind of study that will inform whatever happens next.

DR. TELFAIR: No. Actually Ms. Masny was before me and then I'll go after her.

MS. MASNY: Just a question regarding, again, the public engagement. It said in our readings that the National Children's Study took about six years just in the development of their design and plan. I don't know. Was there any type of public engagement in their whole development of their program and if there's anything that we could learn from that?

And also several of the other initiatives from NIH, the Genes and Environment Initiative, has there been sort of a similar approach to try to get this public engagement? And would it be a worthwhile approach to

review the approaches that they took, and are there any gaps there that we could then fill?

DR. COLLINS: So, with regard to the Children's Study, they've done a great deal of public engagement efforts during the course of these six years in various settings. I can't, off the top of my head, go through the specifics of exactly all of the various constituencies that they've consulted with. A lot of this has been driven by advocacy groups who are very enthusiastic about the idea of getting better answers to why it is that certain childhood diseases occur, and I think that has been probably the strongest voice. But they actually had already initiated, using funds from the Child Health Institute, a series of vanguard centers in specific parts of the country, each of which had a public interaction consultation component. So there's a fair amount of data there that could be certainly pulled out and made available to this committee.

For the GEI and the GAIN projects, these are projects which are focused on specific diseases where there have already been cases and controls studied as part of a clinical research project where lots of clinical information has already been collected and DNA samples have already been collected. The idea now is to apply whole-genome association analysis to those samples. So it's much less of a large population kind of question, but obviously, each of the studies that may end up getting the genome analysis done have already gone through some investigator-initiated effort to recruit those subjects and that's all been IRB-approved and certainly involves both informed consent and some, in many cases, ongoing contact with the participants. But it's really a very different kind of setting than I think what we're contemplating for a large-scale cross-sectional population cohort.

DR. TELFAIR: This is a two-part question, so it's sort of a connect-the-dots thing. The first part that I had, because it keeps coming up in different ways, is can you speak a little bit about the whole -- these are interrelated methods, time, and expected outcomes -- why the focus on these particular types of methodologies? I know it's a pilot study, but in terms of data, in terms of obtaining information, in terms of data collection, and particularly analysis, it's just going to be a little bit difficult given the time frame. But then sort of the expected outcomes of this based on the message that's going to go out.

My question earlier was already asked. Ms. Berry asked about the campaign because it's always effective if the public knows what's coming before something goes out to them. If that's not going to, it sounds like, happen, then the question I have, related to the methods and the timing and then what you expect, is what is going to be the message prior to this going out? That's the first part of the question.

The second part of the question is you said, at least in the initial part you gave to us, that it's a pilot study, which I understand fully. But there's a next step you hint at, which is that there's going to be more input, some other means. Can you connect those dots there a little bit?

DR. COLLINS: I'm sorry. I didn't completely understand your first question in terms of message. Message to whom at what point? I didn't quite get it.

DR. TELFAIR: Well, you're doing a public data-gathering type of process, even though it's targeted, because they eventually will pick groups and select groups. I understand that's up to the purview of whoever applies and dealing with the best way to come about that.

But the methodological research data on this is pretty clear that if you're going to do this kind of work, if there's some information that is given already that the public is expecting, this type of information that comes their way, people are going to ask them about questions. They're sort of ready for it essentially

and they're able to make more informed decisions, provide more informed information.

But then there's the part of analyzing that information, and you have a very short window of time for this. You only have two years to really do this. Those two are related.

But then the whole idea of the outcomes that then will lead to the next steps, you know, the outcomes of the work. And then next steps, which I know this is a pilot, but next steps for some other way of gathering this information, as you allude to here in the information you gave us.

DR. COLLINS: So, in terms of the people who do participate in this consultation process, again, I don't want to prejudge how our grantees will propose doing this, but the usual way involves some sort of initial educational material so that the public who you're asking the question of knows why you're asking the question and what the concept is, so that there are some facts on the table. And then you engage in a discussion, a conversation, either in a focus group format or in something more survey-oriented about what opinions people hold about that. Again, though, there's not in this model any sort of broad, general public education. It's focused on the people who are part of the study.

In terms of where this goes next, this is a pilot in the sense that I would never want to argue that this would be sufficient public consultation at all to actually conduct such a study. But since we don't know if the study is actually going to be conducted or not, I don't know what will come after the pilot until we have a better sense of that. If there is no budgetary enthusiasm for going forward with this, we may never do anything further than this, or at least not for a long time. This may be sort of it.

If, on the other hand, there's some momentum that can be built behind the scientific value of this, then I think every step along the way, in terms of the kinds of things that were on Hunt's slide, about you'd probably want to start actual collection of clinical information and DNA samples on some pilot scale, and you'd certainly not want to do that until you had additional consultation about how to do it and you'd want to be collecting information all the way along during those pilots that you might run in 10 or 15 centers. And only then would you contemplate scaling this up to the half a million or a million people which would be necessary for the full power of the study.

DR. TELFAIR: All right. Thank you.

DR. LEONARD: Francis, on your list of bullets, under optimal approaches to recruitment, you emphasize how to engage family members, but one of the concerns that I see of doing this large population cohort project is engagement, how you engage the uninsured, the under-represented, the underserved. And I think unless those discussions happen, even in this pilot study, I'm very concerned that that's going to be a big hole that has to be filled because I think that those people are going to be the hardest to engage in this type of study. That's more a comment.

The other question that I have relates to terminology, and once terminology is determined, it's hard to alter. But this is being called a U.S. large population cohort study. So that implies that you have questions that you're asking. In reading this draft and participating in the task force, it's not clear whether you're going to be targeting specific diseases or whether you're really creating a biobank, biorepository, medical data, environmental data repository that then can be used for any kinds of studies.

How you start selling this with this public engagement process, I think it's important to distinguish

whether you are talking about building this repository that can be used then for any kinds of gene/environment disease studies or whether you're targeting it to specific diseases because the thought process for those who participate will be different.

Also, through the whole flavor of this report and how we word it, it's very different -- you know, which of these are you doing, and I don't think the committee, SACGHS, wants to be out of line with the thought process of the NIH. So could you clarify that?

DR. COLLINS: Thanks, Debra. I appreciate both comments. In terms of the reflection on the need to be sure we're sampling the underserved and the uninsured, a point well taken. It's sort of in here in terms of communities with special needs and later on in another paragraph, it talks about socioeconomic status and so on, but it could have been more clear that we absolutely need to find out the opinions that come from those sectors of the community.

With regard to the nature of the study, I think your point is very well taken. Maybe we shouldn't be using the "study" word. In fact, many times, those of us talking about this have come to that same conclusion. What we're really talking about is a resource. A repository somehow sounds like something that's a little sleepy and dusty and maybe sort of locked away somewhere and people occasionally go in and look around, but it's not really very active. This ought to be a resource for discoveries about every disease that's common enough to have enough incident cases during the lifetime of the project. And it is not going to be hypothesis-driven. It is not going to be driven by an interest in particular diseases. It's going to be a way, and a very efficient way, to collect the kind of data that you would need to study any disorder that occurs with a high enough incidence to have that kind of power represented.

So, believe me, more hours have been expended trying to come up with a really savvy, eye-catching, acronymic kind of title for this kind of effort, and I don't think we're there yet. But I think you're right. Maybe "study" is not the right term for what we're discussing here. It's a resource and it ought to be a community resource in the sense that it will need to have accessibility to hundreds, thousands of scientists who have good ideas about how to use it. It shouldn't be a closed shop at all.

DR. LEONARD: But then, in talking about this, I think you need to talk about the building of the resource and then subsequent to that, it will be fruitful for all kinds of studies. It might be more saleable if you separate resource or project or initiative -- whatever you want to call it, but a repository is rather dusty -- from all the kinds of things because it also gets to the enormity of the value of what you're really talking about. You can't not talk about the subsequent studies because I think you have to be prepared with access to the data issues and those kinds of things. But I think that this is a huge thing and maybe the committee can discuss this also further.

DR. COLLINS: That's a great point.

DR. EVANS: This is obviously a really promising study, and I keep thinking about ways of getting around what, to me, are the biggest obstacles to carrying it out. And that really, in my mind, is the fragmentation of our health care system.

One of the reasons this is so powerful potentially is its prospective nature. When I see a patient in Chapel Hill, if they've been seen 8 miles away at Duke or they've been seen 20 miles away in Raleigh, I have no idea what's going on. It's awful. And we face a huge challenge that Britain doesn't face, that Japan

doesn't face because of that. This is especially important too with minority populations because their health care is even more fragmented.

I'm wondering if, given the emphasis and the interest in the electronic medical record and that movement that is clearly really important and is afoot, whether there's been any thought to trying to combine in some kind of pilot way this project with that. It seems a natural if you could couple those two things because if you can solve that problem, then I think you can realize the promise of the study, but it's a big problem.

DR. COLLINS: So that is a terrific point, and yes, there has been quite a lot of discussion about whether this could serve as a pilot for an electronic medical record system for the half million or so people who are involved in this study. If you could learn through the process of setting up such a record system on such a research basis where the problems are and where the solutions are, we might be a little bit further towards what otherwise is a rather slow-going, frustrating process.

DR. EVANS: And maybe a deal-killer. Right?

DR. COLLINS: Yes.

DR. EVANS: Just real quickly to follow that up, in the U01, it might be interesting to explore the public's views on that. One of the reasons we have fragmented medical care is people are so scared about privacy. The idea of a universal health card, a single ID card, is something that strikes terror in much of the U.S. populace, rationally or irrationally. I'm just wondering if in this pilot study, whether those kinds of feelings and ways to reassure the population and the safeguards that might need to be put into place would be useful.

DR. COLLINS: That's a good point.

MS. CHEN: From what I've known, there is a study similar to this, but on a much smaller scale, for adolescents in Marin County. It's a prospective study. Basically that study is actually spearheaded by the advocates. There is a high incidence rate of breast cancer in Marin County, and so they had this campaign to find out why there is such a high incidence rate. So they are actually doing a prospective study of adolescent kids, girls. They go to different schools to cover all the bases of the socioeconomic sectors, and then they pick them out and then they just do the watching, taking samples along the way. I think that's probably a patient advocate-driven process, and I think if we wanted to do something similar to that, we probably would need to find out if the patient advocates could engage on it, and if they could, it probably would get this thing working and started.

DR. COLLINS: No. I agree. A study of this sort, if it's going to go forward, you would hope to be able to engage advocacy groups, particularly for the disorders that are most likely to have discoveries made, which would be the common disorders, heart disease, cancer, diabetes, obesity, asthma, hypertension, and so on. I think there is growing interest amongst advocacy groups about this model, although I don't think there's broad understanding yet about what is actually being proposed. At the present time, the way NIH has conducted research of this sort has generally been to set up a prospective study on a particular disease. We have the Framingham Study or the Jackson Heart Study that look at cardiovascular disease. The Cancer Institute runs a long list of specific prospective studies on particular cancers.

Here we're talking about trying to come up with something that is both more global and perhaps more

cost effective because you don't have the duplications of following a lot of people who get a disease that didn't happen to be the one you're interested in. You're interested in everything, which maybe is a bit of a silver lining, by the way, in the budget requirement that if we did this study, we might not have to do a bunch of other studies that haven't been started yet because they would basically be brought in under that umbrella.

We did do a survey and put out an RFI that we got a lot of responses for to see what prospective cohort studies are out there. You've mentioned one and there are lots of them out there that are being already initiated. People are already being followed, sometimes for many years. And it does look as if you might be able to incorporate some of those into this new resource in a way that would take advantage of work that's already been done and money that's already been spent, but it wouldn't really suffice if your goal is to get a true snapshot of the population because there are vagaries of age distribution and geographic distribution and gender distribution and race and ethnicity distribution. You would not be able to populate more than about 25 to 30 percent of your resource with existing studies. The rest would really have to be recruited de novo if your goal is to get a real snapshot of the population.

MS. CHEN: I think to understand how the process occurred, it will help to do a more global understanding of engaging the public because these smaller studies, even though they are targeted to a particular population, but if we could use the information that was generated in those little pilots, how they went into the public and engaged them, maybe we could get some information out of that.

DR. LICINIO: I think the issue of the name of the initiative is -- you spent a lot of time talking about this -- a problem because in this very tight budget climate, if you go to Congress and ask for money for a resource or a repository, I don't know that they're going to be any more inclined. I think the current name, which is "Possible Large-Scale Studies of Genes and Environment, and Common Diseases," is okay because it implies that it's studies in the plural, not like one thing. It could serve many purposes.

But I think it's a bit of a dilemma because if you are strictly accurate, those who don't have a hypothesis, who don't have a specific goal for one question they're trying to address, it is not technically a study. But I think if you try to sell it by any other name to Congress, I don't know you're going to get any money. I don't know if you're going to get any money if you call it a study, but --

(Laughter.)

DR. COLLINS: Well, we had various names but they never really caught people's imaginations. One was AGES, the American Genes and Environment Study. Another was USA HEALTH, the United States Assessment of Heredity, Environment, and Lifestyle for Total Health. But USA HEALTH made some people think of a health insurance company. Sorry, Reed.

(Laughter.)

DR. COLLINS: So it didn't quite get above the threshold. But if you all want to put your thinking caps on and come up with something that captures the significance of what's being proposed, without having any negative buzz words like "study," that would be great.

MS. AU: Francis, obviously this study will need to be a multi-institutional study, multi-agency study. How much of that input would be put into this pilot study for multi-agencies, multi-institutes?

DR. COLLINS: We certainly, in the process of going through that 18-month study design effort, had input from a large number of NIH institutes and multiple Department of Health and Human Services agencies and even some from outside the Department like EPA. For this particular RFA, we also got input from several other NIH institutes, and we certainly used the discussions that had already happened in that previous 18-month study, plus the discussions that have happened around this table with the Secretary's advisory committee.

So I think we have a general sense of what other groups are interested in learning from this, and certainly, as we go forward with this, we are welcoming the opportunity to interact with all of the other agencies and institutes that have an interest, which is a lot of them. I think that will be a pretty open environment.

DR. WILLARD: I have Ellen and then Debra.

DR. FOX: I thought it would be useful to update the committee on what's going on with the Department of Veterans Affairs. It's been mentioned a couple of times. You have in your packets a recent press release that I'll elaborate a little bit on what's going on.

As I've previously reported, the Department of Veterans Affairs is developing a genomic medicine program that builds on ongoing genetic and genomic research efforts by the Department. The plan is really to make use of VA's unique assets, which really are in contrast to some of the problems that have been mentioned here in terms of, for example, we have a very comprehensive and sophisticated electronic health record system in the Department of Veterans Affairs. We have a very large, stable, and loyal patient population of close to 8 million enrolled veterans. We have a centralized and integrated national health care system which is not fragmented and we do have the ability to standardized throughout the system. And we have an already robust intramural research program that really allows us to apply uniform standards across the country.

So to take advantage of this, we are planning to develop what will be the largest adult genomic medicine research and clinical resource -- we are calling it a resource not a study -- in the United States. The program is expected to involve the collection and storage of over a million patients specimens, together with relevant demographic data and links to individual clinical records. So the aims of the program are to improve not only the care of veterans in terms of their clinical care in research mode but also to benefit the health of the nation as a whole.

The VA genomic medicine program is proposed to have national management in Washington, D.C., with coordination among the Department of Defense, Department of Health and Human Services, and other agencies and resources in VA's central office. The genomic medicine activities will be conducted at multiple sites throughout the VA health care system.

The FACA committee has been established. The notice appeared in the Federal Register on March 16, and you have a list of the members of that committee in your packets. The committee will provide advice to the Secretary of Veterans Affairs on the scientific and ethical issues related to establishment, development, and operation of a genomic medicine program. Specifically, the committee will assess the potential impact of a VA genomic medicine program on existing VA patient care services, make recommendations regarding policies and procedures for tissue collection, storage, and analysis, and make recommendations on the development of a research agenda, and recommend approaches by which research results can be incorporated into routine medical care.

The time lines in the budget for the program have not yet been established, and I'll continue to keep the committee posted as events unfold. We're early in the development. And I will try to answer any questions if you have any.

DR. TUCKSON: First of all, thank you, Ellen, for that. Mr. Chairman, I want to just make sure that the committee is cognizant of the clock. You've had an opportunity now to ask a lot of questions to Francis and so forth. There was a lot of stuff that our committee chairman has put out there for you as well. So as the next comments are made, based upon all that we've heard -- and I was glad to hear from the VA and that was an important observation as well. As the next comments are made, I think you need to really start tailoring in on what do you want to do by June, what is the advice to the subcommittee. You've got to lock in now because it's getting late. I'm always the bad cop. That's the problem.

DR. WILLARD: You were just one person too soon. Debra has a final comment.

DR. LEONARD: No, no. I was going to say shouldn't we get on with our development of recommendations because the time is running out.

DR. WILLARD: Thank you, Ellen, for that information. I think I would lead this off with a general question for the committee members who weren't on the task force, as well as those who are on the task force. The question is, especially given our now push to try to get this finalized by the June meeting, whether the draft report and its list of issues is essentially too all-inclusive and that the risk of being at the 1,000-foot level is that we may make it more difficult for ourselves to finish it by June, or are people, in general, comfortable with the level of depth and the comprehensiveness and the breadth of the report?

DR. TUCKSON: By the way, speaking of comfort, if you've not noticed, there ain't no break. So this is not like kindergarten where you've got to raise your hand. You've just sort of got to roll.

DR. WILLARD: I assume that means you'll be leaving us, Reed.

(Laughter.)

DR. TUCKSON: There were a few people who were wondering where the break was.

DR. WILLARD: So let me throw that question out because I think we do need some feedback and it will help guide us for the remainder of our time here today in terms of how deeply we want to drill and how broadly we want to be sticking flags in the ground. So let me open that up. Joe.

DR. TELFAIR: Yes. One of the things it seems to get at that, because it will kind of put some structure around it, is two things. One is besides prioritization of the issues, it's also what will be the time. If we had to walk through each one of these in terms of setting priorities, would you also set a time frame related to that particular priority? I was wondering if that is reasonable to also have some discussion because it is a lot of information. It is a lot to try to cover, and it's hard to make that judgment whether it's way too much information because then you have to decide what you're going to cut and what to keep, what not to keep, what to modify, and that sort of thing. It seems a lot of time and effort has gone into pulling all this information together. Prioritization seems the first thing to do and then some kind of time frame around. In other words, if you do a study, can you build on the study over time and add parts to that as you go about doing the work itself, sort of a study, discovery, study, discovery, that sort of thing?

DR. WILLARD: Well, I'm not sure what you're asking in the sense that we're not trying to design the study. We're making recommendations.

DR. TELFAIR: No, no, I know, but in terms of structuring the recommendations, structuring what would go into the report and how we get it done, all I'm suggesting is prioritization is the first step in terms of making recommendations of what is a priority over another. But I'm also wondering whether or not there needs to be some temporal aspect to that as well.

DR. WILLARD: Well, certainly one approach could be -- and we don't need to do this part today as long as people are receptive to the idea and responsive to the idea of doing it from your desks at home -- is that we could prioritize the issues, essentially get a sense of the committee by a vote. That's how we dealt with our original prioritization process two years ago. And within the issues under each one of the policy sections, simply let the committee decide which seem to be priority 1, priority 2, or priority 3, and that, at the very least, would help us flip and flop different sections of the report in order to focus more intensively on the ones that everyone agrees are the critical issues.

But I think Kathi and the rest of us on the task force can take a look at whether any of them are temporally dependent on other issues, because there's no point in having something listed fifth if you have to do that one first before you get to the others.

DR. TELFAIR: Right, and that is my point. You can't just prioritize. You also have to look at the issues related to logistics and how would those would fit together logically. It may be that you would set a prioritization for things that are there. So, yes, thanks.

DR. HANNA: When I was trying to put the information together that was coming from many different sources, the way the report is structured right now, I did try to organize it temporally. So the first question is research policy, go/no go, and then sequentially designing the study, what should you think about. As results begin to emerge, what kinds of things should you think about because I thought that there might be some logical checkpoints along the way where you might have different kinds of public engagement mechanisms, but you certainly want to consider the full time line even from the get-go. But I tried to organize it that way because I thought there might be different approaches you would come up with depending on where the study is, either from its initiation to its final conclusion.

MS. CARR: I think also, as part of the recommendations section of the report, you could provide additional advice to the Secretary about all the issues that are discussed and identified and say that in order to begin to think about whether to do such a study, the very first question that policymakers will need to address is the following. I think if you do that, you will probably find that the order parallels the order as Kathi has organized it. So that would also mean that you wouldn't have to do a rearrangement of the actual report too if you focused on the recommendations section.

MS. AU: I was wondering if there is a chance to break up the report to make it more palatable. We know what things need to be done first, like the public consultation. You need a general overview, of course, of what the project is, but if we're looking at things like getting something to influence maybe the Secretary for the budget year, getting something in a smaller chunk as a report and then doing chunks of the report as we work through this really large, large issue, and making it more palatable for people so it doesn't have to be this huge report on everything under the sun.

MS. CARR: Well, certainly there will be an executive summary of the report. That's definitely something we know we would need to do. Rather than that being a total sum of the report, that could be the things you want to highlight as well.

MS. AU: This is such an extensive study and such a huge issue and there are so many things that we do want to add into it and putting in detail. If you did it as parts, that there's a priority of what you need to do at the beginning, and then we can get more and more in-depth as we obtain more information from the pilot study and from other studies that are done and do the report not as a single report, but as parts of a report so that we can address the issues fully.

MS. CARR: So that would mean you would sort of indicate to the Secretary that the committee is going to be continuing to work on this for a long time, and that for right now, as the 2008 budget cycle begins, we want to tell you the following about all of this, so focus only on that. Hunt, I don't think the task force really considered that approach. That's kind of a new thing.

MS. AU: I think only at this meeting we were told that, for budget considerations, we need something by June.

MS. CARR: For 2008 I guess, would that be a focus on public consultation then for the spending of additional resources?

MS. AU: I think it would depend on what the committee decided was the starting and the endpoint could be for the first priorities.

DR. WILLARD: Well, let's remember, we're not designing the study, nor are we necessarily making a recommendation of go/no go. We haven't been asked that question. We're simply supposed to lay out on the table for the Secretary, to do with as he wishes, a series of possible approaches that would help him get to the question to the go/no go point. So even in terms of what might be valuable, what might go into the FY '08 budget, that could be absolutely anything. It might only be public consultation, but it might be early pilot projects, and presumably Francis and others would be deeply involved in that process, and our input isn't necessarily asked for nor expert in that regard.

MS. CARR: Hunt, I think you've made a really good point. Sylvia, this is a very complex thing in that we've identified many issues. In some ways, I sort of think personally that it's incumbent upon the committee to let the Secretary know. Look how many issues there are. It is rather daunting, but it might be important for the Secretary. I'm sure he already has some indication of this, but to see them all laid out in a big report and in a thoughtful way I think might be of value.

DR. LEONARD: I agree with you, Sarah, that having the whole picture presented is a better way. I'm afraid that if we focus on what we think should be done first that we're not giving him the perspective of the entire project, and a lot of the discussions that have already gone on on all the different areas of concern that need to be addressed.

DR. FROHBOESE: Just a quick comment. I definitely second Debra on that and do feel that a comprehensive approach is very important.

But also, given the fact that there seemed to be very frequent, new developments and new projects that

are starting, the VA project, a couple of other projects that have just started within the past couple of months, I know that there's an appendix that talks about other efforts, but other initiatives that have started both on the federal and private level I think will be really key to highlight here and how any efforts that we might be involved in would be coordinated with or integrated with those efforts.

DR. WINN-DEEN: So, first, I wanted to say I sort of like the outline here where you're starting to make arguments in favor of the different things. It reads a lot like the sample ballot that you get that describes arguments in favor of proposition 103. What seems to be missing is the other side of the story. I think to have a balanced report, we should help the Secretary understand both the arguments in favor, as well as the arguments against that he may have to overcome and deal with. So I think that's an important aspect that should be in this, at least brought to his attention.

I also think in view of our sort of ongoing role to urge coordination of effort and all of that kind of thing among agencies and within agencies, that it would be very useful for the Secretary to receive a comprehensive view of what's going on already, as Robinsue indicated, both within his own organizations as well as in some other places like the VA, so he can get a sense of the fact that this is sort of a continuation or an evolution from a series of smaller studies that have set the stage and led us to the point where we're just about ready to consider something on this scale and scope. It's not just coming out of nowhere.

So I think from that point of view, that perhaps someone from NIH could be really helpful in terms of writing a section that really describes how the different things that have gone before -- you probably already have this in your word processor there somewhere, Francis -- have led up to this and the lessons learned and how various compositions of things that are out there already can be used to leverage moving forward on a study of this magnitude.

I think you get to the point where you're eventually going to have to sell this to a funding agency, the U.S. Congress. You're going to have to sit on the other side of the table and think about what arguments you would want to have in front of you for that funding. They have to be very persuasive arguments, and you can't just tell one side of the story. You have to tell the whole story.

DR. WILLARD: I believe we have about 45 minutes at this point.

There are a group of slides, the first of which I've got up there now, which were essentially straw man either mechanisms or approaches. They're written essentially in terms of being recommendations or could be couched in terms of specific recommendations. These are on the slides that are in your folders as well.

There are four related research policies, this being the first of those, and these came a little bit from the task force and its conversations. It also came from staff and its deliberations, and they're literally just ideas thrown out for people to either respond to or to guide us as we go on to the next stage.

So this first one really points up the need for consultation with the scientific community as well, not just the public at large, to address, in particular, the issues of leveraging the half dozen or more existing efforts that are already out there.

I'll start this off and then others should chime in. I'm not sure what the approach is here except to broadly

consult where no man has consulted before.

(Laughter.)

DR. WILLARD: But to ensure that the broad scientific community is part of that. Obviously the scientific community has been engaged at one level already in the task force that Francis had.

DR. TELFAIR: I'm just wondering whether this is actually -- let's see. I'm trying to put this as euphemistically as I can -- a redundant recommendation because it sounds to me like everything that has been said, this has been done already at some degree. You spent the time with a number of different groups and committees and you've spent it in information-gathering and you constructed that, and this committee has come up with this report, as well as, Dr. Collins, you've come up with the RFA you put out already. So I'm wondering whether or not this has already been done.

DR. WILLARD: Certainly it has been done with a group of scientists, including some that, as I understand, were nay-sayers in the beginning and then came along with the process and became believers, if I remember the story correctly. But there is a large number of people in the broader scientific community who either know nothing about this right now or what they know, they don't like because they view this simply as a challenge to their funding for their own priorities, and this doesn't happen to be very high on their list of priorities.

So Francis couldn't possibly have taken on all of them, nor would he necessarily want to, but the Secretary may wish to have some mechanism that allows one to touch base with the broader community.

DR. TELFAIR: Well, then I'm wondering. I understand, okay. Well, then do you need to be a little more specific then?

DR. WILLARD: No. We don't need to wordsmith here. As long as Kathi and Sarah are taking notes, they'll get the sense of how to revise the language.

DR. TELFAIR: All right. Then I put this as a question related to this particular slide. Do you need to, even if it's broad, have a little bit of a good working definition of what broad means?

DR. LICINIO: If I remember well, when the Human Genome Project started, it was during like a dry funding period and there was a lot of practice like FASAB sending letters to you. From what I've seen now, the level of opposition to this is actually smaller than to that back then. Am I delusional or is that true?

DR. COLLINS: I think it's a little hard to draw the comparison because I think Hunt is right. A lot of scientists haven't heard about this possible project, and maybe as it gets more broadly discussed, the intensity of those who are unhappy because of this concern about the budget might go up. I don't know.

Certainly you have to be careful here. If you're intending to obtain unanimity from the scientific community about going forward with something, that will mean you're not doing anything very ambitious or interesting. So the goal of consultation of the scientific community ought to be clearly laid out ahead of time, that it is not necessarily to convince everybody that this is worth doing. You won't succeed at that. The Genome Project, when it started, was probably opposed by about two-thirds of the scientific

community. Yet, looking back on it, it was the right thing to do.

DR. LEONARD: In this, there isn't really a detailed presentation, if you will, of the scientific utility of large population resource. Has that process been done? That's different than opinion polling or selling. But is there hard scientific data and how can that be presented to the scientific community at one level, to the public at another level? Because I hear a lot of skepticism as to whether you really will attain the power to be able to identify genetic markers, et cetera.

DR. COLLINS: Terry Manolio, who is a well-regarded genetic epidemiologist, is actually writing a review on just that question for Nature Review's Genetics, which I hope will be out in a couple of months, which really does try to go through in pretty rigorous fashion the scientific arguments for the value of this data and how it's different from the kind of data that you would get from a case-control study or other study designs.

DR. LEONARD: Can we get that?

DR. COLLINS: Yes, as soon as it's in a form where you could call it finished. It's under construction at the moment, but it should be, yes, distributable pretty soon.

MS. MASNY: This is just a question. I think in the report, when we read it, there was the question of whether the research policy overview would be that of a hypothesis-driven versus sort of this resource, and it seems like that was answered. But I think the other question that may go to this slide about the broader scientific community input is the issue of the pooling of current case-control or cohort studies or do we construct a new association study. I think those were sort of the those in favor of. That's where the two sides went and whether something like this could be addressed in this light.

Or the other approach is that since we're doing a pilot with the community engagement, would there be one way to actually look at using some of the current existing case-control studies to maybe answer some of the clinical questions that Debra just brought up, the clinical utility?

DR. WILLARD: I think the issue of clinical utility is obviously not an easy one to address, especially when you're dealing with, if it takes a million subjects to know whether it's going to work, then no one is going to have the data to do that. I think it's useful to see the review that Terry is putting together.

But, Agnes, you're absolutely correct. There are well-respected scientists out there who say this is nuts and we could do 10 case-control studies of a reasonable size before one should do this. And that's an open debate that we should acknowledge.

MS. MASNY: Would it be feasible to actually do a feasibility study maybe with a few of these people that already have registries maybe for a specific disease population to actually see if some of these gene connections with the SNPs and the variations that we're trying to zero in on is actually feasible to do even in a smaller population?

DR. WILLARD: Well, Francis, correct me if I'm wrong, but certainly those studies are being done and they're well underway.

DR. COLLINS: So, for instance, the Framingham Study is about to engage in whole-genome association

analysis of a substantial fraction of the participants. The NCI is funding whole-genome association analysis of large prospective cohorts on breast cancer and prostate cancer. So you will start to see some of that data generated.

Again, one of the goals of a prospective study -- I don't think I have to remind this group because you've thought about this a lot already is to identify what the environmental contributions are and what biomarkers might exist in terms of prediction of disease before disease is actually diagnosed. Those two things come very poorly out of case-control studies, if at all. Hence, the logic behind arguing that you really need both these study designs if you're ultimately going to get the answers we need.

MS. JOHNSTON-LLOYD: I just wanted to point out that we're addressing the vulnerable populations of the uninsured as part of the U01, if they are to become part of the pilot study, and reaching out to the community for engagement. One positive outcome that could result from the study is the fact that we would increase the understanding of health information around genetics among these populations who we know have limited literacy skills. To me, to get them to participate, they're going to have to first understand it, as we all know.

So I would think that that might be something -- I don't see it specifically, but on the bullets, it said charge to the grantee, that that would be a key, important component in that. That really goes along with the Secretary and the Surgeon General's real caring about the health literacy of the people in our country. That's kind of a side comment, but it does tie in.

DR. WILLARD: Debra, and then I want to move on I think.

DR. LEONARD: I move that we agree to this and like move on others. I don't know whether anyone disagrees with this.

DR. TUCKSON: All in favor?

(A chorus of ayes.)

DR. TUCKSON: Nays?

(No response.)

DR. WILLARD: The others are even easier, notwithstanding the wordsmithing. This one here relates to the potential value of a collaborative model of project leadership and management. It speaks to the issue that many different agencies and units within HHS have an interest here and even already have a thumb in the pie. He will have to use his leadership to figure out how best that should go forward.

Any comments on this? Debra?

DR. LEONARD: Is this getting at the heart of academia and the single investigator promotion process? The interdisciplinary nature of this and the way academia currently works is by the single investigator doing hypothesis-driven. So part of what has to be done here is the engagement of academia, and I don't know how you do that. But this has huge implications in engaging the scientific community. If they still have to get promoted in academia based on their grantsmanship, then anyone who's not the principal

investigator on a project is not going to participate. So I think this is coming in other ways to academia with the whole NIH Roadmap, but I think that's particularly significant here.

DR. WILLARD: The HHS Secretary is close to all-powerful, but to expect him to reach into the hornets' nest of U.S. academia --

DR. LEONARD: But it's the engagement and having them understand where this goes. That discussion is already ongoing in academia. Maybe this reflects back to the first one that we just voted to pass. I mean, that's part of the engagement of the scientific community also. That's one of the fears that scientists may have in going down this road and investing so much because it will be multi-disciplinary approaches and grants that will be given to access this resource.

DR. WILLARD: I think there are points there that we can certainly highlight in the report because that's a point well made.

DR. HANNA: Yes. I think this particular recommendation was -- maybe it's not clear enough -- meant to focus on, I think, the governmental level not at the academic level.

DR. WILLARD: This is NIH, VA, et cetera.

DR. HANNA: This is HHS-wide. Right.

DR. TELFAIR: I'm adding to this because I was going to say that already there are several of these types of announcements that are made from multiple institutes and multiple agencies that collaborated to co-fund these projects. To just give some grounding to this, and maybe add that to the recommendation to look at some of these other successful models that exist, that would help a lot there.

DR. WILLARD: Okay, those are good points. The next one -- Mr. Chairman, I don't see the need to vote on these as we go because we're not at that stage yet.

This one is even, I think, easier to consider.

DR. TUCKSON: By the way, just in the interest of time, though, if we sort of say okay, move on, just note that that means you're saying yes because we're not going to go back and play around with this.

DR. WILLARD: Well, we'll play around with the wording, but we're not going to --

DR. TUCKSON: Right.

DR. WILLARD: This is your opportunity to speak.

This one relates to broader consultation and looking for possible leveraging with the international community and the private sector. I think to some extent, both of those are already ongoing, at least from some perspectives, but it's well worth having the Secretary focus on that approach. Debra, you look --

DR. LEONARD: I agree completely. One of the things that I'd like to suggest is that if such a biobank would be created in the U.S., one of the benefits of having cooperative or collaborative arrangements with

other biobanks is for cross-validation. So you do a study in the U.S. and you use similar cohorts from other biobanks then to validate whatever markers are done. If investigators in the U.S. don't have access to those other biobanks, then that cross-validation won't happen as readily. So that may be one of the things to explore in these collaborative types of agreements.

DR. TUCKSON: Hunt, what I would also say is I think on things like this, first of all, it's always important to state the obvious over and over again, given that we are in D.C. But I would say this. And we're not here to write the language, but I think if you just as a general template for these things, where they are ongoing, given Debra's point, where things are happening, I think if we say because the committee is interested in facilitating this and that, we are aware that people are looking at such and so and so, therefore we hope the Secretary will take advantage of that and help to move those ongoing activities forward more rapidly. That's sort of the spirit, I think, of what a lot of these are getting at. So we're sort of saying there's a reason why we want you to do these things. We're aware that certain things are happening. We are here to say that those are important things which we hope that you will pay attention to and thereby not have to reproduce the wheel.

DR. WILLARD: Okay. Any other comments on this one?

(No response.)

DR. WILLARD: The fourth of the approaches laid out under research policy, the fourth and last one, relates to attempting to ensure that there's widespread and ongoing support for a stable investment in this. I'm not sure how much of that is under the HHS Secretary's purview because the budgetary process -- correct me if I'm wrong, Francis, or anyone else among the ex officios -- you can't fund a 10-year program up front without continuing to revisit that every FY. Is that correct?

DR. COLLINS: Every year is a new year.

DR. WILLARD: So it can be spelled out, but it will take an ongoing series of broad consultations and making sure there's broad engagement every year so that it continues to have support and doesn't get stopped before it could be of any use.

DR. LEONARD: Are there lessons to be learned from the Framingham Study and the way that that got -- I mean, that's been continuous for years, and there are others.

DR. COLLINS: Since 1948. That's right.

DR. LEONARD: All right.

DR. COLLINS: You could also look at the Genome Project, a project that had to be conducted over 13 years to succeed. Basically once you get it started, you need to ramp up to whatever the stable level of funding is, and that has to find a home somewhere that becomes part of the base so that it's not one of those things where you really have to start from scratch every year. But there is an opportunity to debate whether the base is too high or too low. So Framingham is funded by the Heart, Lung, and Blood Institute, so it's in their yearly funding where that support comes from.

DR. WILLARD: Other points or comments here?

(No response.)

DR. WILLARD: Then we have two slides, three possible approaches relating to research logistics, one dealing with the issue of stratifying the sample population. This is not solely a research logistic question because this clearly reaches across into the public engagement domain at the same time.

Does anyone want to comment or address that first one? These two are obviously related.

DR. WINN-DEEN: I guess I'm a little confused because I thought we were trying not to have a stratified population, but have a population that would be representative of many things. So I'm not sure really what even this means.

DR. WILLARD: Well, I think the issue that has come up in many quarters -- the Human Genome Project is a good example and the HapMap is a good example. We have the genetics and genomics community that's making some arguments about the scientific rationale for or validity of various descriptors. Then we have another branch of the government that every year has you tick off boxes that say which one of those groups you think you belong to. I think even in the planning for this -- again, we're not presupposing how such a project may unfold, but there are identifiable population groups where everyone puts up a flag and says we've got to make sure we get enough from that group or we need to find ways of getting full engagement from that group. So there is a stratification in terms of recruitment and trying to make sure the data are readily applicable to "identifiable" subgroups, depending on how you identify them.

DR. LEONARD: Well, I guess I would rather say it for assuring diversity in the projected sample population. Stratifying to me is not what you're striving for here. What you're trying to do is, when you do this 500,000 people, you've got enough representation from all the subgroups that you can make statistically valid conclusions. You're not trying to go out and say, all right, we're going to, a priori, say we're going to collect X number of people who say they have a family history of heart disease.

DR. WILLARD: No. I think this is more stratification of population groups, not clinical groups.

DR. EVANS: And I think you have to have stratification or you get stratification bias if you don't delineate. So that's a statistical necessity to stratify your populations, or you end up with bias.

DR. WINN-DEEN: Yes. I guess I just object to the word "stratifying." Can't we use diversity or something?

DR. WILLARD: You're absolutely right. This is prospective. So you're not saying we want 20,000 cases of disease X because that's not the purpose of a prospective study, but you do need to identify we want 100,000 members of this population subgroup, or that's the goal.

DR. LEONARD: One of the concerns I have with at least the stratification scheme that was presented and developed through the NIH committee that got together and then one of the speakers that came and presented to us -- there's a lot of stratification based on census markers, if you will. So that takes into account potentially economics and race, ethnicity, but it doesn't necessarily reflect genetics.

But if this is a gene-environment-disease study, what about environmental stratification? I know different

areas of the population, but one of the speakers said why not stratify based on lives near a toxic dump, doesn't live near a toxic dump. So I think that this scientific discussion is really important to make sure that we're not stratifying in a knee-jerk way, which I don't mean to insult that committee that did a lot of hard work. But I'm not sure that the environment stratification is really well thought-out, and maybe that's something that GEI could also be considering as ways to stratify by environment, even though "stratification" is the wrong word.

DR. TELFAIR: Whenever you engage in the process of trying to include certain groups of persons, at least initially you always run into the problem of just making decisions about who to include and not to include. It seems to me that in terms of taking a step back and making the recommendation, it would be better to have a clear and consistent definition parameters for systematically identifying and assuring representation of the desired samples, and then let whoever comes on board after that make the decisions about how that will be done because if you do it that way, it leaves room for decisions to be made. I think the argument here has been made pretty clear. You don't want to have preselection when preselection itself may be flawed in some way. You want to be able to get to a point where you can make some really good decisions. So I recommend that.

I know we're not trying to tweak the language, but it just seems to me leave it open to the point where you can allow whoever this consulting and scientific community group comes together to make some of those decisions, but really give them some directions about what I hear everyone saying is about representation. So I would recommend that as sort of a way of tweaking the language here to cover both the first and the second bullet.

DR. COLLINS: Again, just in the name of not starting from scratch when there's already, I think, at least a straw proposal out there, the work group that looked at this tried to balance the number of different parameters that you could try to match the study population with the general population without it becoming logistically impossible and came up with, as I remember, seven or eight, which included age, gender, race, ethnicity, urban versus rural, geographic location in the U.S., which has some relevance to environmental exposure, as does urban versus rural, socioeconomic status, level of educational achievement. Those were all down there. If you try to go to a longer list, you pretty soon end up with very small numbers of individuals in each cell, and then you lose power. So you have to kind of think about the balance between those issues.

But it was something the group thought pretty long and hard about, and certainly I would suggest starting there, but I'm not assuming that that's the right final answer.

DR. WILLARD: Other comments here?

(No response.)

DR. WILLARD: That's useful.

The last bullet under research logistics is dealing with best practices for how one gathers and collects clinical information over the course of the study. Some of this, of course, is related to the electronic medical record prospect. Some of this deals with samples, as well as data information.

Again, I don't think it's particularly controversial in the sense that any group who is contemplating this

has already done much of this as they've moved ahead.

DR. WINN-DEEN: So since this is envisioned to be a long study period, over which time, technologies, and markers and lots of things may evolve, can we put something in here to encourage the data tracking and all of that to also be open to changing technologies or new methods? I think some of the older studies suffered a little bit because the way it was done at the beginning of the study has evolved over time and now you can't really do that same imaging test or whatever in the way it was done 10 years ago or 20 years go. So there has to be some way of dealing with the fact that technologies evolve over time or even if there's a new something that you want to measure.

DR. WILLARD: There must be similar language in whoever planned the Space Station out there that we're currently building, but it has to change and will continue to change if they find whichever pieces are missing.

Other comments on this logistical issue?

DR. LEONARD: Should that in some way have a statement tying it to the EMR initiative?

DR. WILLARD: I've already flagged that. You're absolutely right.

Regulatory and ethical considerations. This is a very long one, but it essentially invites the Secretary to convene a group of many representatives who are represented by the ex officios here and others in order to examine all of the sort of regulatory and ethical issues and come up with a list which would add a set of approaches that would be necessary.

Again, I suspect this is already being done in some quarters, but Ellen?

DR. FOX: The wording seems to imply that implementing the regulations would deal with the ethical issues, and I just want it to be clear that a lot of the ethical issues you have to deal with are not really answered by the regulatory requirements in this case.

DR. WILLARD: So one might want to separate those two.

Other comments?

(No response.)

DR. WILLARD: The other side of consulting with that group of experts is consulting with the study subjects themselves on an iterative basis around the issue of the protections that they either need or feel they need or both. Again, it anticipates that this is a multi-decade process here so that there will be substantial changes both in terms of what is of concern today may not be of a concern later and vice versa.

Comments?

DR. WINN-DEEN: So is this really aimed at having an ongoing ELSI component that is there? You know, it's not just at the beginning where you've asked the questions and then, much like the Human

Genome Project, had an ongoing ELSI component. I mean, is that really what this recommendation is?

DR. WILLARD: That could certainly be one such mechanism.

DR. WINN-DEEN: Okay.

DR. WILLARD: Joseph.

DR. TELFAIR: This is just to enhance a little bit of what's there. It seemed to me that this recommendation also deals with the power relationship that's going to emerge out of this. If you are paying attention to at least the last part where their recommendation is for enhancing protections, it means that the subjects in the project are actually making recommendations to those who are studying them on how to improve aspects of the project. That sits very well with me, but I'm just concerned about where it would sit with those who are actually conducting this work and whether or not you need to make that real clear, that this is going to need to be considerations of the power relationship between those who are being studied and those who are actually conducting the study.

DR. WILLARD: I think it's fair to say that there probably are a number of models that one could consider and, in fact, are probably being considered or implemented by other countries that are further down this path in terms of what level of ongoing discussion and engagement with participants is in place. I don't think anyone contemplates sort of saying, well, great, you're on the hook, we don't need to talk to you. But there are obviously different levels and frequencies with which one might want to work with the participants. And frankly, some participants may not want to be involved on a regular basis; others may choose to be.

DR. TELFAIR: Yes. This kind of approach to engagement, which is participatory in itself -- the science around participatory work, though, really involves the question of letting those who are subjects make decisions to what level they want to be involved. There's no question about that. So there are models that exist. There's a whole area of work that actually models this very well. It seems to me that we can, as we go into this, just make recommendations for whoever is doing this to look at those models. I agree with you. I'm actually enhancing what you're saying, but there are models right here in our own country. That is done in participatory research models that involve this. So I would recommend that we put this as a part of this part here if we're ever going to do this. There's another part coming up that we also would add that too as well.

DR. LEONARD: So in a way, this goes back to the resource versus study language and objective of this project. If it is a resource, then the managers, the leadership of that resource basically act as honest brokers, if you will, to anonymize data to allow access to investigators. So that may be another advantage to having this set up as a resource rather than as a study because then some of the inducement or subject interactions are reduced because they're just creating a resource as opposed to wanting them enrolled for certain purposes. There's less conflict I think.

DR. WILLARD: Then in the public health realm -- the approaches are beginning to look very similar, but now in the public health realm in terms of evaluating, disseminating the findings with those who have expertise in public health. Here I think both this and the next one deal with this dichotomy of whether this is a study which is going to have results or whether this is a resource and the results actually come out in a nearly infinite number of other studies that will be funded in order to examine the data. This, if

anything, calls that question into stark relief. I mean, at some point -- and I'm sure Francis wouldn't disagree -- this either is a study that has results that people will examine or it is simply collecting all of the data and those who have been made available to scientists to carry out further studies, future studies. It has to be one or the other. I guess it could be both, but it either has to be one, the other, or both. It can't be vague.

DR. LEONARD: In calling it a study, you basically skip over all the access to the resource issues because it's a study and so there will be results coming out of it as opposed to building the resource and then how do investigators -- the equitability issues of access to that as scientific resource, et cetera.

DR. COLLINS: So, again, we talked a lot about that in previous discussions about the study design. I think the basic idea was you would collect a certain amount of clinical information and medical record information and physical exam information and genetic information and environmental exposure information on everybody who's part of this. The database that gets generated by this resource would be accessible to anybody who agrees to a certain number of stipulations about not trying to identify who the participants were.

A lot of the early sort of associations of genes, environment, and disease would come out fairly directly of that database. But people who are really interested then in digging into a particular disease would be able to mount a much more sophisticated analysis in a sort of case-cohort model, identifying the incident cases that appeared, going back and determining more sophisticated information about those affected individuals perhaps with imaging, perhaps with additional laboratory studies that you couldn't possibly afford to do on the entire cohort.

So it's a little bit of both. The idea would be you would have a basic set of information that in itself was pretty powerful about diseases that occurred at a high enough frequency to have power for analysis, but that would be sort of a foundational floor and then you'd build on top of that a lot of disease-specific, more intense investigations that were mounted by specific investigator interests.

DR. WINN-DEEN: Can you just clarify? Because now I'm a little confused.

DR. WILLARD: Who are you looking at?

DR. WINN-DEEN: Francis. What you just said was you envision it as being a database rather than a bioresource.

DR. COLLINS: It's both.

DR. WINN-DEEN: Okay, thanks.

DR. LICINIO: I have a quick question about the issue of anonymity even if you call it a study and if there is like an initial study that will mostly be a resource that will lead to a lot of new research.

But one issue that I think is even more worrisome now than what I was aware of before is the issue of anonymity. I don't know if you saw, this past weekend or the one before, the New York Times Sunday Magazine had an issue about sperm donors. So just through the information that people put there like describing themselves like who you are and the family background, you just get some of the key features.

I'm sure that in this study there are going to be much more identifying features than you have just in the description of a sperm donor. And you Google that and you find exactly who the person is. Many people have been identified. You need like five or six identifiers and you Google that and you find the person. So that I think should be a key issue of the initial engagement process because for those who participate, I don't think you can guarantee anonymity with all of this information available about the person.

DR. COLLINS: I think that's absolutely right. I think any guarantee of anonymity, if you're talking about this degree of data collection, is not something that you could legitimately put forward. There's going to be a risk.

DR. EVANS: Not only that, but what you're collecting is the ultimate identifier.

DR. COLLINS: Right.

DR. WILLARD: I think the parallel with the Human Genome Project is pretty legitimate here. Yes, the Human Genome Project was about collecting a resource, namely sequence data, which are now available for everyone to enjoy and study. But it was a study at the same time. There were data being collected and analyzed in order to have that sort of first pass of what the genome was and what it would mean. All of that was part -- correct me if I'm wrong, Francis -- of "the Human Genome Project" before you blew the whistle and said that's now done and we move into another phase.

That makes me feel better. I was afraid I totally misunderstood the Genome Project.

(Laughter.)

DR. WILLARD: The second of the public health ones. Here again, this assumes because this is asking for or at least considering the possibility that project leadership would convene on a regular basis to review research results. This again, depending on how you read that, it's either to review the results of a study and potential answers to questions or it's to review the collection of the data and the availability of the resource, dealing with sort of logistical issues there. This is coming in the section under public health, so the intent is to be in the former category, but depending on whether examination of research results is or isn't part of the actual initiative or project or whatever it's called, this one may need to be reworded a bit.

Comments here?

(No response.)

DR. WILLARD: And the last one under social implications is, in fact, one of the most specific ones, which I think we probably should discuss appropriately, which is that the HHS Secretary would consider establishing essentially a standing advisory committee, perhaps independent of, perhaps not independent of the actual leadership of the project itself, that would periodically look over the shoulders and examine the social implications of the project working with the public at the same time in order to be sure that there is no new set of concerns that are coming along. This is a little bit of a watchdog effort.

And what isn't stated here is who that standing committee would report to. Would this report directly to HHS? Would it report to whichever agency is going to lead this project, et cetera? And one could

imagine different ways of putting that forward. So I think for us, it's to get a sense of whether some kind of a standing committee on social implications is a good idea. We can, of course, leave it up to the Secretary to decide who ought to be advised by such a standing committee.

DR. EVANS: Would this be separate from oversight within the effort itself about privacy, IRB issues, or would it be part and parcel of that?

DR. WILLARD: I think the intent of this is that this would be sort of on the outside looking in, which would be complementary to what you're describing, which is a very large effort on the inside that would be involved on a routine basis.

DR. TELFAIR: Along these same lines, the question would be would this also be influenced by the mechanism or the construction under which this project would be funded? For example, if it's a contract -- well, it depends on the city. If it's a resource or if it's a study and then who you're accountable to, in other words, who's providing the funding, that will influence decisions of how this committee is both constructed, what it's made of, and how it functions.

DR. WILLARD: You're absolutely right.

DR. TELFAIR: So that would be the thing that we need to consider when we're looking at this as well.

DR. WILLARD: Other comments here. This is the one that's closest to a specific recommendation for an action that the Secretary might take. I don't know if the ex officios, Ellen or Francis, have any reaction to this and whether there's a role because within the NIH or the VA, you would have your own advisory groups already, of course, and the question is, is there any value in having an independent, freestanding standing committee?

DR. COLLINS: I think any program of this sort would have to have this kind of input from a group that was clearly not influenced in some way that rendered their opinion suspect. So they'd have to be on the outside looking in.

But whether that is something that would happen naturally in the process of setting up a project of this scope -- it might very well -- whether this is something the Secretary would need to set up separately, whether this might actually be a function of SACGHS at some future time, because some of the things you're talking about here sort of sound a bit like SACGHS, just in the name of avoiding committee proliferation, it might be good to point out that there may be ways to do this that don't require setting up a brand new, separate committee, that there may be aspects of this function that could be conducted by existing groups.

DR. FOX: I guess it also would depend on the relationship between the agencies and the nature of the collaboration. If there's really a true collaborative effort, then the committees that are dealing with each agency might not be sufficient to step outside and oversee the entire effort, in which case this would be important.

DR. WILLARD: Other comments from anyone?

(No response.)

DR. WILLARD: Well, those are the sort of straw man approaches and lead-ups to potential recommendations that the task force came up with and staff came up with. The question is, have we forgotten anything? Do any of you have your sort of favorite approach or recommendation that is now missing? Debra?

DR. LEONARD: Well, I kind of made an outline of the project and all the different parts of it, and many of these recommendations cover those different parts, but there are certain ones that seem to be not covered in any recommendations that we may want to think about adding. So the public engagement and feedback process is covered by 1, 3, and 9. If you think about setting up the biobank, there's enrollment, which is covered by 5 and 6, if I number these sequentially. There's medical data that would be gathered. That's addressed by 7.

Environmental data will be collected. That's not really addressed by any of our recommendations. I think there's tons of work to be done there, and so we probably need to encourage support of GEI or other kinds of environmental data collection initiatives, how that will be done, engaging the scientific community or whatever.

There's also then specimens and genotyping, and do we know everything that there is to know about specimen handling and storage and do we want renewable resources? Is that fairly well already known? And we may not need a recommendation there, but we may.

And then the ethical, social, regulatory issues are addressed by recommendations 8 and 9.

Then if you have the biobank set up and if it's done this way, how do you access the biobank? And there seemed to be fairly straightforward ways of doing that through grants, applications, et cetera. So I don't know if we need a recommendation for that.

Then once you have results, there's an emphasis on communication to the public in the recommendations, and that's 10 and 11.

But there seems to be a hole of how do these results get translated into clinical practice. That's a big hole in my mind because that's why we're doing this, is to influence medical practice, to have better patient outcomes, et cetera. So we may want to think about how these results will be translated into diagnostic uses or risk assessment uses, therapeutic strategies and preventive strategies, because I'm not sure prevention is really very well developed.

And then there's overall funding, which is addressed by 2 and 4, and then external oversight is addressed by 12. I guess we're assuming that there will be internal oversight set up, which we discussed, but there is no recommendation about that.

So those would be the areas that I think where we may want to think about additional recommendations.

DR. WILLARD: That's a very useful structure and a way to think about it. I'm sure Sarah will reach for your list that you just drew up.

DR. SCHWETZ: There are three points that I would like to make that cut across your recommendations. One of them has to do with achieving diversity among the population that you would like to eventually

recruit. You're well aware of the resistance of some subpopulations, particularly the minority populations, to participate in research. And I think if you don't have some effort ahead of time, you won't achieve it here either.

One of the things that we've learned from OHRP, as we've tried public outreach programs particularly with the American Indians and Native Hawaiians and Alaskan Natives and other populations, is there are structures that have been built up to protect these populations from researchers because of the abuses of the past. If you try to bypass those, you will not be successful in reaching those populations.

So one suggestion would be to figure out a mechanism by which you can work through their existing infrastructure to allow them to reach their populations and not the investigators in order to achieve success in those populations.

Another one has to do with seeking regulatory input. I would suggest that sooner or later some of these regulatory issues need to be faced. In the same way with the National Children's Studies, if they're not addressed early, they become significant stumbling blocks later on. And I would encourage that you would form some kind of a regulatory group that can be advisory, but if that group gets together and makes recommendations and puts it up on a website or some other way, it won't be very successful if you don't have the IRB community and the investigators involved because if all they see is something on a website, it doesn't tend to get their attention, as opposed to developing these best practices and some of the thoughts on how to make this study proceed to allow the study to proceed without hurdles, get those communities involved early on and don't just let NIH and OHRP and FDA write some guidelines for how to deal with these regulatory hurdles that doesn't involve development by the people who are actually going to have to make the decision about the protocol. And that's the IRB community.

The third one is the public will be skeptical, and you've talked about that. One of the reasons the public might be skeptical is because they don't know what's going to happen with their samples when they get it in the bank. And I would recommend that you consider developing guidance now to address the question of how can samples be used out of the database or the biobank so that the people who are considering participating would know at this point, for example, the requirements for IRB review for any studies that would be based on their samples. Do IRBs have to be involved or not and under what conditions can these data be deidentified so that perhaps they're not human subjects research from then on? I think you might find the public to be more understanding and interested if they know what's going to happen down the road and what protections they will have, as opposed to simply contributing genetic information, samples, and then wonder a few years later what's happening to it without the knowledge that they have some protections.

DR. WILLARD: Thank you for that. Other comments?

(No response.)

DR. WILLARD: Well, Sarah, we're at the point at which, together with Reed, we were supposed to determine next steps for the task force and for staff to further draft this. Is Reed hanging in the hall, do we know?

MS. CARR: He had to step away for a few minutes.

DR. WILLARD: Okay. I think in terms of next steps, let me go through at least one possible way of proceeding, which is that Kathi, working by herself initially --

(Laughter.)

DR. WILLARD: -- take what we've heard this morning and work that into another draft which can then be cycled past the task force, which may want to have another one of its phone conference calls in order to deal with that, and then get that to a point where -- I mean, at some point, we have to be able to say now it's ready to go out to the public for public comment. Does that version have to be approved by the full committee or can that be a task force version if the committee so chose and gave us that latitude?

MS. CARR: I think it can be a task force decision if the committee feels it wants to put that --

DR. WILLARD: So then let me throw that question out for the full committee on whether the full committee is sufficiently happy with what you've seen and what you've heard this morning that you have some degree of confidence that the next draft will be sufficiently mature to go out to the public under the name of the full committee. Let me turn it the other way. Does anyone object to that?

(No response.)

DR. WILLARD: The chairman is happy.

DR. TUCKSON: The chairman is happy with it.

DR. WILLARD: Okay. And then having gone out for public comment, the public comments, Sarah, would come back in.

MS. CARR: Correct.

DR. WILLARD: And the task force would consider those?

MS. CARR: Well, staff will summarize them and the task force will review them and decide what to do about them in terms of the report.

DR. WILLARD: And that will take us then to a near-final report with near-final recommendations that would then go out to the full committee for final action ideally at the June meeting. Do I have that right?

MS. CARR: Right.

DR. LEONARD: Hunt, I think something that the whole committee needs to decide upon is, is this going to be presented as a two-stage process of building a resource and then accessing, or is it going to be studies, plus the resource? Because it's different in how you frame the report.

DR. WILLARD: Oh, I don't think that's up to us to make that call. I think if Francis were here, he would even say it's not up to him to make that call. This is just the early days and who knows how it's going to come out? I think we have to inform the Secretary of the sensitivity around those issues and simply highlight those issues that are relevant to sort of plan A versus plan B versus plan C.

DR. LEONARD: I think that needs to be clarified then in the report, that there are these different scenarios of how this could be done.

DR. EVANS: But I think that regardless of what you call it, there will be results coming out. Right? Even if it's just research. There will be studies embedded in it. So I think we have to deal with that larger fact that these things are going to have to be dealt with because it will be a de facto study even if we call it a resource, don't you think?

DR. LEONARD: Right, but some of Dr. Schwetz' comments were if you define how you access the anonymization of data, those kinds of things, that's a real step that hasn't been defined. When you call it a study, it's kind of a resource and a study all in one as opposed to then accessing later for studies, either additional or --

DR. EVANS: Yes, I think those things will have to be addressed. Right.

DR. WILLARD: But our job is simply to point out to the Secretary that that's an open question.

DR. LEONARD: I didn't mean that we were deciding how it was --

DR. WILLARD: Then he will have to decide on it, or he through his office will have to decide on it. I'm less concerned about study versus resource because, as Jim said, at some point they merge. But the deidentification versus identification issue is absolutely fundamental. Either there's information potentially going back to these half million or million participants to guide their future health care or there isn't, and that seems pretty fundamental.

Does anyone not like the process I just outlined, which is coming up with another draft, the task force taking it to the point at which we can go to the public, the task force and staff working with the public comments to get to a final draft or a penultimate draft that will come to the committee prior to the June meeting? So the next time most of us will see it will be June.

DR. LEONARD: Can it go to the committee at the same time it goes to the public? I think that that's reasonable so that they have time to provide input as well.

DR. WILLARD: I realize that you have precious little time, except those of you flying from the west coast, to look at this version of the draft prior to this meeting. So I think that's a good point. We can certainly anticipate that.

Any other comments from anybody?

(No response.)

DR. WILLARD: I'm sure our chairman is listening. He's coming in just now. Let the record show that we finished our work 5 minutes before we were supposed to.

DR. TUCKSON: I've been monitoring you carefully in the other room and observing everyone personally. Congratulations. Good job.

We are going to have lunch, which is made and specifically wrapped for each of you individually in bite-sized portions, you'll be happy to know. Now, the deal is we've got to come right back. So what time do we start again? 1:30. The people who are not on the committee go downstairs. So we start again at 1:30.

You guys are terrific. That was difficult but a satisfactory conclusion. Thank you.

(Whereupon, at 12:27 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:34 p.m.)

DR. TUCKSON: If you think you're going to have any more breaks, you're wrong.

If that Huntington Willard will come on, we'll get started. Past staff people are holding him up.

By the way, I really appreciate the end of the last discussion. I'm sorry I got caught in the middle of that crazy phone call, but we really were monitoring and trying to do two things at once, but I had a little problem I had to resolve.

We're very excited to have Emily take us through the update on the Pharmacogenomics Task Force. Let me just remind people of a few logistics. We take this until 5:00 unless you're terrifically wonderful when you can be done at 4:30. But past history is it will probably be midnight before you get out of here.

(Laughter.)

DR. TUCKSON: There is no dinner tonight. We're trying an experiment to see what happens when you're left to your own devices. If, after having not had a dinner meeting tonight and you're all so sad, that you want to resume --

MS. CARR: It's not a meeting.

DR. TUCKSON: Is anybody sad that we don't have the dinner bacchanalia?

(Laughter.)

DR. TUCKSON: It's not a meeting. Believe me, anybody that's monitoring this from the government and the sunshine rules or whatever it is, there's not a single person that has anything of substance to say at any of these meetings. It's just fun and crazy and tomfoolery.

But anyway, if any you really miss the tomfoolery and would like us to resume it, let Sarah know because she's the tomfoolery coordinator.

So we will end at 5:00 and then we resume again at 9 o'clock tomorrow. Know that you've got to be down in the lobby with the crack security team and NIH external police force which will be there to check you out by 8 o'clock again tomorrow. So that's the same drill as before.

By the way, if you all want to hang out through some informal ways tonight, feel free to share names and numbers. Thank you.

DR. WINN-DEEN: So what I wanted to do for you today is to just give you an update on what the Pharmacogenomics Task Force has been up to. Just as a reminder and a thank you to all the people who serve on the task force -- from our own committee, that's Jim Evans, Kevin Fitzgerald, Debra Leonard, Julio, and Hunt -- and then a number of representatives from the ex officio side as well, trying to keep a balance and make sure we get input from all the folks who have a stake in this.

Historically we had our first session on this subject back in June with the goal to identify what the key issues were through a series of presentations and to identify areas for further fact-finding through the committee meetings.

We had a second information session in October where we heard presentations on some of the financial issues and the implications of pharmacogenomics for racial and ethnic groups. We outlined a

report and started discussing a number of possible approaches.

In today's session, we're really going to try and focus on moving ahead with a meeting report from the committee, and we have the pleasure of being briefed by FDA on the just hot off the presses FDA guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Disorders. So Steve Gutman is going to provide us with a short update.

Since the October meeting, the staff particularly has been extremely busy pulling together background information from a huge variety of sources. We have looked back at the SACGHS discussions, the presentations, a series of recent reports from areas outside of SACGHS, and in addition, the staff conducted and the agencies within the federal government were kind enough to respond with quite a bit of information in terms of what is going on already within the federal government, our goal being, again, to act as coordinators and to identify if there are overlaps which could be put to more efficient use, as well as if there are significant gaps where nothing is going on.

So in terms of the outside sources, staff went through a number of reports from outside groups that had looked at this particular subject. The U.K. has been particularly active in this through two different groups. The Nuffield Council on Bioethics, as well as the Royal Society, have both published quite extensive reports on pharmacogenomics. There's a book on ELSI issues edited by Mark Rothstein that was used that has some nice primary data on sort of the way people think about using these tests and how they feel about them.

So that information was pulled together and really digested down into a number of topic areas. You'll find that -- it's a series of white pages -- in your book under tab number 6. So we tried to, as a starting point, gather what thoughts had already been put into the public domain, so to speak, from other groups and see how that balanced with what we might be thinking.

Then we did a survey of federal efforts in pharmacogenomics that were organized by major issues and need areas that this committee had previously identified. The staff used both information gathered directly from the member organizations, as well as things from their websites and literature. That is a very long document also in the white pages of your tab 6. What is in your table folders is a very nice summary, which you might want to pull out for our discussion, where Fay has summarized under each of these different issues and needs what's going on in the different agencies. So it also references the more detailed information.

But also the task force asked staff if they would pull together sort of a third column here, which is this possible areas for future focus. So we probably will have some discussion about some of those areas as well.

So in terms of Federal efforts, we divided the efforts into a number of areas, the first of which was research and development. As we had heard the presentations over the last year, it became obvious that there is still a lot of research to be done in this area. So the specific needs were that there is perhaps a need to identify a different approach, a novel research team approach, given the fact that a lot of this information is involved with drug trials, which are typically run by the private sector versus NIH or other public kind of sponsorship of trials.

We raised the issue of how to get studies on already-marketed and generic drugs run, and we'd

like to have some discussion of what it might take to get some of the things that are already on the market into studies that would result in the data that you need to decide if there should be a pharmacogenetic test.

What is the evidence of effectiveness?

What are the models for utilizing a test in an economic benefit sense? The last thing the health care needs is another cost of a test to be put in the way of getting health care. So how do we balance that out?

And then there obviously needs to be some coordination between the drug companies and the test developers. These are two separate groups who are not typically working together today. So we need to figure out ways to encourage that coordination.

Both the NIH and the VA support investigator-initiated research on both new and post-market therapeutics. So there are some investigators who have applied for grants under various programs. The NIH has the Pharmacogenomics Research Network, which was a very targeted set of RFPs and grants given out for this express purpose, to find associations and to validate them.

And the FDA has also been quite proactive in working with both the diagnostics companies, as well as the drug companies, to really start to understand their respective viewpoints and understand how, through working with FDA, those viewpoints and needs and desires can both be part of this and can be coordinated through an FDA review process.

Similarly, the CDC has the EGAPP program, which we're well aware of.

AHRQ has the DEcIDE Network and AHRQ also has a research initiative in clinical economics. I'm not sure if there are any of these economic incentives yet that are focused on pharmacoeconomics, pharmacogenomics, but it certainly is a place that such studies could be funded.

In addition to just gathering basic scientific evidence, we all know that there is another component that needs to happen before the practice of medicine is affected. So you could have great science, you can have all the other ducks in a row, but if you don't understand how to change clinical practice, then there won't be the end result, which is the desired result, which is to improve health care.

So there are certain barriers to integration that we need to be aware of as well. So you can't just say, well, this SNP is associated with better response to drug X. You have to provide the information that the clinician needs to translate that. Does that mean that you give a different dose to different patients based on their genotype? Does it mean that you don't give that drug or you only give it to a certain subset? You have to provide that guidance to them and teach them how to use it.

Different medical specialties have different levels of receptivity to this kind of thing. I'd say traditionally the oncologists are the great experimenters. They're willing to try anything new because their tools are still so limited that they never have what they'd really like to have to help patients. Other specialties are much more set in their ways, and there's a lot higher level of show-me attitude that you have to overcome before you can affect clinical practice.

As we're well aware, you need to also make sure that tests can be reimbursed and properly paid

for in order to have something be part of the routine practice of medicine.

Clinical practice is also highly affected by the sort of best practices guidelines that are put together by a variety of groups. AHRQ and HRSA are two of the government groups. There's, of course, also within most physician organizations varying medical practice guidances that are issued in terms of when and where a test should be utilized and how it should be utilized and interpreted. So all of those things need to be addressed.

In the realm of pharmacogenetics where you could presumably be genotyped at any point in your life and then that data utilized later to formulate decisions on whether or not you should receive a drug or at what dose you should receive a drug, there's a need to figure out how to make sure that that test information stays with you over your lifetime. So once you've had the test, for whatever reason it was ordered initially, how do you make sure that the next time a physician needs that information to deal with your health care it's available to them. From that point of view, the infrastructure that electronic medical records and data standards is working on I think is relevant to this particular area as well.

We've got a number of other infrastructure things going on within the federal government. I'll let you read all these different things, but part of this is aimed at trying to make sure that you have all of the information that you need to make a good decision about a patient at the time you need to make that decision.

Then there's the whole oversight issue, who decides how and when pharmacogenomics should be utilized. The FDA has worked extremely proactively with the pharmaceutical side to encourage them, as they do a lot of their biomarker research, to submit that research data just as that, as research data, so that we can start to understand among clinical trials if there is any pattern that's emerging that a specific biomarker is predictive.

I think the fact that there was a guidance document issued, a tremendous amount of consultation with the pharma industry that resulted in a finalized guidance document last fall, really is a model for how we can start to deal with the public/private issues and encourage groups, that normally would have perhaps a more adversarial relationship, to start to think about a more coordinated kind of relationship.

The hole right now that I see in the oversight. We have, as Steve is going to talk about, a new guidance document on what you need to do to get a pharmacogenetic test approved. We have the guidance document to pharma. What we don't have yet is a guidance document that really puts those two things together and says under what circumstances will a test be required, under what circumstances will there be a labeling change in a drug. If a test comes on the market, does that go back and affect a drug that's already there? We have examples where those things have happened in the community, and I think through the process of those things happening as sort of pilot studies, it's possible that FDA -- I'll let Steve address this when he talks to the group after I'm done. Maybe starting to think about, now that they understand a little bit different scenarios, how they could formulate at least a draft guidance on when and where labeling changes actually get made on existing drugs or get incorporated as a requirement in a new drug upon release.

So we also have, within the Federal agencies, different mandates. FDA's mandate is to assure safety and efficacy.

CDC's mandate is more of a public health mandate, and they've been focusing on assuring testing quality both through the CLIA program, as well as through a program to help develop quality control materials for genetic tests.

And then, in terms of trying to organize how research information can be "standardized," there's a whole interagency effort on microarray data, now to report it, how to quality control it, how to normalize it among studies, all of these kinds of efforts so that you can use data sets from different studies to pool together and draw conclusions.

Again, science is only part of it. If we really want to have science implemented, there needs to be an education component. We need to educate patients so that this is not some strange word that they hear and they get a test, but they don't know really what that means or how good data is going to be used. Are they going to have to give informed consent for pharmacogenetics testing or is this outside of the realm of the informed consent world? And we need to educate the physicians to help them understand when it's appropriate to use this in their own clinical practice.

To that end, NIH has produced brochures to help inform the public about what pharmacogenomics is. NIH and HRSA both provide funding for NCHPEG's educational efforts, which are aimed at health care provider education for the most part, and AHRQ also has a center for education and research on therapeutics which is helping to educate providers.

When you think about how to make a public health impact, one of the things that needs to be in place is an effective surveillance system. Now, FDA has an adverse event reporting system, which has already been in place for a long time.

The other three areas are not as well surveilled in terms of, once you get through a clinical trial, does the effectiveness of the drug in the general population it's being used to treat the same as it was in the clinical trial population. Are there any unintended consequences of that? And are there any strange utilization patterns? We don't track that really at all. Probably the pharmaceutical companies have the best data on utilization patterns, but they typically use that as part of their marketing. It's their proprietary data. It's not something they normally would be sharing.

So, as I mentioned, there's a number of different mechanisms in place. Obviously, CDC's overall mission to protect the health and safety of all Americans. That's at a higher level, a lot more generic level, I guess I should say, than FDA's which is focused more on specific health and safety related to drug use. And then we've got work going on at AHRQ as well.

There was a desire from this committee, I think as part of our regular work with the agencies, to assure that there's coordination and attention and/or awareness of what's going on between all the agencies, and that was part of the reason that we did this survey of what's going on at the agencies, both to allow all the agencies to know what's going on outside of their own world, as well as to inform this committee. So we hope that that will be a useful exercise in promoting communication. We'd like to see some mechanisms put in place to promote data sharing among studies funded by different agencies within the HHS and the health care system in general.

Now, the good news is that personalized medicine, whatever that means, is part of Secretary Leavitt's 500-Day Plan and is on the FDA Critical Path Initiative, which means that there is high-level

interest in seeing the promise that pharmacogenetics offers implemented where it's appropriate.

NIH has stepped up to the plate and funded the PharmGKB database, and that has been out there, I think, for about four or five years now. We've seen some good evidence of sharing of information among the agencies, and the CDC has their Human Genome Epidemiology Network up and in place.

We have a number of ELSI things that we could consider making recommendations on or at least drawing the Secretary's attention to. These are pretty much the same kinds of things that we talked to him about on most subjects, but for sure, we want to make sure that we don't encourage any health disparities either on socioeconomic bases or on racial bases. We want to make sure that the whole informed consent and privacy protections that are needed are in place.

Debra will talk a little bit tomorrow about the impact that gene patents could have on this field in terms of availability of assays.

I think we need to keep in mind that genetic exceptionalism is also an issue in pharmacogenetics; that is, your response to a drug or the dose you should take is not only driven by what your underlying genetics is. What concomitant medications are you taking, what is your medical condition, what food are you eating? There are other things that can affect that, and so it's not a strictly deterministic thing, although it does provide some informative information to help guide therapy but it shouldn't necessarily drive therapy.

Of course, we've got ELSI programs going on all throughout the NIH. So most of these issues are being addressed already. We have diversity guidelines for clinical trials in place and specific groups focused on areas like treating children and making sure that minority populations are correctly included in any trials.

So the plan for today's session is to identify the broad areas for focus of our recommendations. What we've tried to do in the yellow pages at the front of your book is to draw together in each of these subtopics -- if you turn past the first three pages, there's a thing that says background for the session. What we've tried to do is pull together in that section the previous things that SACGHS has sort of identified, what's going on in the federal government, are there gaps, and are there some proposed recommendations. So I think what we'd like to focus on today is an assessment of whether we've got all the bases covered, are there things that we've missed as a task force --

DR. TUCKSON: Emily, hold on one second just to make sure everybody got that. There are two page 1s. You've got a couple pages of page 1. Go past that and then you'll see another page 1 and it will say "background information."

DR. WINN-DEEN: Right. The short version in the front I think was an attempt to do an executive summary, but it sort of leaves things out, and I think the one that has the background really has all the pieces. So it has what's going on in other groups, what's going on in the federal agencies, what was SACGHS concerned about in the past. And then this is an area where we can sort of pull that information together and consider making some recommendations.

The task force and staff have inserted a few "proposed" approaches as starting points for our discussion. These are just that. They're starting points for a discussion. They're not, by any means, a set-

in-stone recommendation or anything along those lines. We want to get the full committee's sense for what are the things that we really need to be talking to the Secretary about, what are the things that the Secretary of Health and Human Services can effect directly, what are the things where we need to encourage coordination between HHS and other groups, and then try and formulate recommendations.

I don't have a slide on this, but we're fortunate that the Office of the Assistant Secretary for Planning and Evaluation, ASPE, has found some funding in their bucket and has offered us this funding to support a report-writing by the Lewin Group. After the yellow pages, there's an outline of what the draft report would be. Actually it might even be after the federal pages. It's a two- or three-page outline.

The goal is to have a draft report to the task force by May 1 so that we can review it. So we definitely want all input that we can get today that might need to go into that report or affect the way that report is structured. Our goal would be to bring that draft report to the June Secretary's advisory meeting for both review of the report, as well as for review of first draft of recommendations to insert in various spots in that report, much as we did for coverage and reimbursement report.

So that is sort of the goal of what we're about today to try and ascertain whether there are some things that we need to do further work on, further information-gathering, and then try and rough out the priorities for what we want to say to Mr. Leavitt.

I think that's the end of mine. I'm going to turn the podium over now to Steve Gutman, who's going to go through and give us a short update on the FDA draft guidance for industry, which you also have at the very back of tab 6. Sorry. I should also say Steve's slides are in your table folder, if you want to take notes on that.

DR. GUTMAN: Good afternoon.

As Emily indicated, the Critical Path Initiative remains a very important work product at FDA, and that initiative is aimed at the notion that FDA should, in a proactive way, work to remove obstacles from the critical path to bring new cutting-edge medical products to the marketplace.

In the original white paper that Dr. Woodcock actually sponsored about two years ago, biomarkers figured prominently and, in fact, were explicitly mentioned several times. It's not your father's Oldsmobile anymore. Biomarkers were for the purpose of diagnosis, but in fact, there was what isn't a completely revolutionary but a somewhat revolutionary construct that biomarkers might actually be very important in the development in the early life cycle of selecting drugs for development.

In fact, recently that critical path has been reconfirmed. There's been a lot of publicity from the agency about a collaborative partnership with a nonprofit group in Tucson called the Critical Path Institute, and there has, in fact, recently been the publication of an opportunities list which, if you'll look at it, would demonstrate that we are either very broad, very catholic in our thinking, or perhaps a bit delusional --

(Laughter.)

DR. GUTMAN: -- because it's very extensive and there's something there for everyone. I urge you to search for those.

My work group, OIVD, the Office of In Vitro Diagnostics, is frankly a small cog in a very large wheel, but we do have a real passion for this work and that passion's most recent outpouring is in the presence of the guidance document, which you all have and which is also available on the Internet.

That draft guidance was published in February of this year. There is a 90-day formal comment period, so we're about halfway through the comment period. In fact, if you look at the guidance, it will explicitly tell you where to comment, and we are, fact, very anxious to get comments, very anxious get either general or specific comments to ensure that that document is all that it can and should be.

To recap the history, FDA first issued a broad document on multiplex testing in February of '03 and did, in fact, get very lively comments on that document. Perhaps the most recurrent theme or leitmotif in those comments was that that document may have been too ambitious and may have been overreaching and that we might do well to break that into two pieces to try and maintain some immediate focus and then to go for the more garden variety test -- I hesitate to use the term because there's nothing at all garden variety about this testing -- and then to worry about very complex permutations of tests and complex proteomics and perhaps microarrays, and particularly expression microarrays a little bit further down the line. We have taken that advice.

If you look at this guidance, there are several things that might strike you. One is it is a draft guidance that has been reissued as a draft guidance because we do think there has been so much substantial change. There has been a narrowing in the focus. We haven't forgotten the expression array part. We did what we could do and now we have to start moving on towards the even harder stuff.

We're from the government, but we're willing to take help if there's anyone in the other public or private sectors who would either like to write a first draft, write an outline, or provide any support, intellectual or written.

The purpose of this draft guidance is explicitly noted in the up-front introduction, that we're trying to help shorten development and review time lines by creating a road map for sponsors and creating a certainty in the kinds of data expectations that we're likely to put on the table when we see a new product. We obviously are very anxious to facilitate rapid transfer of new technology from the research bench to the clinical lab, and we are actually anxious to do what we can do, not as a primary educational but certainly as an agency that's interested in risk communication and safety communication, to encourage the informed use of pharmacogenomic and genetic diagnostic devices.

The guidance is directed at our usual clientele, manufacturers, particularly the diagnostic companies that know and love us and that are traditional submitters, traditional sponsors of new diagnostic devices, and of course, the FDA review staff. That's explicitly noted up front in the title. But, in fact, it probably has a broader audience than usual because there is a lot of development and a lot of interest among venture caps. There's a lot of development and there's a lot of interest among pharma companies. And these will tend to have less knowledge base about what a diagnostic is, what a diagnostic regulatory pathway might be. So this is actually also geared towards rather nontraditional sponsors. And last and perhaps not in the least bit least, this is directed at academics, at government researchers, at entities that might be funding translational research, so that they might have some target for how they might spend their time and spend their money.

Among the key elements, first and foremost, is intended use. Any of you who've heard me talk

about our regulatory process over the years of the life of this committee will know how important and how passionate intended use is for us. It is, in fact, the basis for our entire risk calculation. It drives everything about the review process. Intended use will determine the kinds of risks we would attribute to a device. The intended use will determine the regulatory threshold, we would expect, needed to bring a device to market, and the intended use will, frankly, dictate the kinds of data that we would expect to see.

So we've clearly posited the importance of intended use and the options. We frequently suggest that people be relatively non-ambitious and look for focused and clear intended uses. We've indicated the need for explaining to us the clinical purpose and the target population for the new product.

And then we've acknowledged -- we've not solved -- the challenge of addressing the issues of rare events, the issue of low prevalence of some disease processes, and defining performance for predictive tests if the entity that's being predicted, if the outcome that's being predicted, in fact, is occurring far in the future, how challenging that will be to sponsors and how challenging that will be to us.

The document goes on to describe device design and to explain the kinds of questions we will likely be asking about the device design. This is not rocket science, but it's also not for amateurs. We are looking for information that will describe what the device does. We are looking for information on samples, for information on methods, and for information on controls.

A good FDA review, of course, would be nothing without a preoccupation with the analytical performance of the assay, and so we're likely to ask about the core studies that demonstrate analytical performance, look at issues of accuracy, look at issues of precision, look at issues of specificity, when appropriate, look at issues of levels of detection or measurement, and of course, look at cut-offs.

We are interested in putting on the table in a clear, forthright, and on the front burner the important issues of the mechanisms of software and instrumentation that will drive the methodology at hand.

We are very interested in the clinical performance as well. As you know, for many analytes, for common analytes, for analytes like hemoglobin or like sodium, we actually allow extrapolation from analytical to clinical use with relatively great facility. It would be absurd for us to take a new submission for hemoglobin and ask the sponsor to please demonstrate that it's associated with anemia. That might not be true with the new Steve Gutman gene. We might be very interested in understanding the eccentricities with which it is associated, and we're likely to ask all kinds of nosey questions.

If you look at this document, you will notice that it would be kind to say the clinical section is a bit laconic, that it's terse. It references itself in the STARD initiative, so certainly it uses what I would characterize as the fundamental, most important road map of modern laboratory diagnostic science. So if you don't know the STARD initiative, please look at it on the Internet.

It also defers a bit to the concept paper on co-development of drugs and diagnostics, which has very detailed sections on clinical performance, both the clinical validity and the clinical utility of the test. That guidance document is under revision and I think we'll probably, in some more clear and comprehensive way, chart various options for the clinical characterization. The concept paper is not a bad starting point. If you haven't looked at the concept paper, please do and particularly look at appendix C and D, if you're interested in issues related to clinical performance.

Then last, but again not least, what would a good FDA review be without obsession over labeling and truth-in-labeling, and that labeling includes all of the parts of our Code of Federal Regulations starting with intended use and ending with communicating the appropriate performance parameters.

FDA has a fairly comprehensive program that it brings to the table when it does regulate any medical device, certainly an in vitro diagnostic medical device. It has a comprehensive device authority for ensuring minimum data and labeling thresholds are met prior to marketing of a new diagnostic. It has quality system regs to assure that there's consistency in the manufacture of that product over time, and it has both mandatory and voluntary reporting obligations that it puts on laboratories or on health care users so that if something goes awry, the FDA can hopefully collaborate with the sponsor to fix whatever what's gone awry. Of course, if the company is not as enthusiastic we are, then we will coerce the company to fix what has gone awry.

This guidance document is now joining an arsenal of other interesting guidance documents, all addressed in many ways towards this same fundamental issue, the issue of co-development. The voluntary genomic data submission -- the primary ownership of that product is in the Center for Drugs, but it is shared by us, and that either pharma or IVD interests, in fact, do have -- I know you're not supposed to use the term, but I'll use it anyway -- a safe harbor in which to explore interesting data very early in the life of a product to play, to inform themselves, to inform FDA, or to create some increased certainty about what regulatory and scientific options might be on the table.

We have a, I think, probably too long, but nonetheless very well-intentioned and very nuanced and very -- I'm highly biased because I was very involved in drafting many sections of this, and I have colleagues who were very involved in drafting many sections of this. But we have a concept paper on the co-development of drugs and diagnostics, which isn't quite on the mark, but has many treasures in it and is an interesting starting place.

We have also snuck in along the way a very nice statistical document for test method evaluation that explains core issues like sensitivity and specificity and tells you what to do when you can't find a gold standard. So it's also a treasure.

In terms of our next steps, we do intend, hopefully with input from the public, to continue to develop and publish guidance documents to clarify regulatory routes, that we continue to promote informal or formal early interactions with sponsors so that we can clearly understand what's coming in the pipeline, we can clearly make sure we have the requisite expertise. We turn to other Federal agencies for requisite help, that we make sure that our panels have the appropriate scientists to provide the scientific grounding we may need for cutting-edge diagnostics. In CDER, they have the voluntary genomic data submissions. In my center, we have what is called a terrible name. It's called the pre-IDE. What that means is a protocol review.

Now, a pre-IDE is about the only work product we still offer that's free, and we ask companies to bring in their protocols, hopefully before they've started their studies. I use the example that the protocol in the pre-IDE process is a little bit like a pop quiz except we give you the questions ahead of time. The companies get to answer the questions ahead of time and submit them so we can tell them whether the answers are right or not. In fact, if the companies don't like particular questions, we can argue about it before rather than after the study has gone on, and we can clarify where we agree and where we disagree and, if nothing else, try to make the pop quiz not at all a pop quiz, but in fact a very well-defined path to

market that will allow us to work quickly and allow the company to work quickly and allow us to reach what I believe is our mutual goal, slightly different perspectives, but mutual goal to get good products onto the market quickly.

We continue to look for ways to better communicate our existing regulatory requirements. As you know, as I've said at this group before, we do have a dual mission to promote public health and that's by getting good products out quickly, to protect public health. That's by ensuring that the products are properly labeled and, in fact, if they're bad products, they never make it to market. There is a tension in these dual goals, and we attempt to address that through good science and by maintaining regulatory focus. It would be my view that if we do maintain the right regulatory focus, you can take us off the table, but you can't take the table away. And so the pesky questions we're likely to ask will still be in the room.

Thank you.

DR. WINN-DEEN: So I'll let Steve return to his seat and then I'd like to open the floor for discussion, if there are specific questions anyone would like to ask Steve on the basis of his presentation. Why don't we take questions for Steve first, and then we'll have a discussion of where the task force is and where we should go moving forward.

DR. TUCKSON: By the way, Emily, just as we get ready for those questions for Steve, let me just make sure again that I'm centered. Given the background that you gave us a moment ago and the idea of the Lewin paper, which we've got laid out in terms of what they're going to write for us, at the end of the day, again from our discussion with the committee now, ultimately can you just reframe, just capsulize again what it is that you will consider to be a success at the end of this day when you've gotten it from us? Is there a way so we know exactly what you need to take your report to the next step?

DR. WINN-DEEN: So I feel like we've got a pretty good set of background information gathered at this point. What we would like to do is make sure, if there are any holes, things that we didn't consider, other reports or anything that people are aware of, that we should include in the background information to get that in for sure.

What we really want to do in the second part of this session is to go through each of these areas and discuss the potential questions to answer or recommendations to make and sort of get a sense of the committee whether we're on the right path with those things, are there other things that people have a burning desire that this group should address on that subject, and really to open it up beyond the task force for input.

DR. TUCKSON: So again, just to make sure I got it right. You've laid out a set of things that you consider to be the menu for what would be this part of the contribution to that overall report, which the Lewin folks are drafting out. So you've got a menu there.

And I think what you're making sure that we're focused on is are there any glaring sins of omission in that menu that you don't see. And then as we go through each of the items on the menu, if there's anything that you want to throw out because you think it doesn't belong there, and then within the discussion of each of those, is there some color that you want to give it, some more granular focus on each of those points that we would want to bring forward. Am I on the right track?

DR. WINN-DEEN: Would you like to chair this?

(Laughter.)

DR. TUCKSON: No, no. Being the dumbest one at the table, I just always have to kind of go back and make sure that I'm locked in. All right.

DR. WINN-DEEN: Yes, okay. So here's your shot. James. Sorry. Did you have a question? Questions for Steve?

DR. GUTMAN: Before you ask a question, actually I left a response out because you asked about re-labeling of drugs. Actually Debra had asked earlier about re-labeling of drugs. I actually am not sure I can explicitly answer what will happen, particularly since the re-labeling of drugs does not occur in my center. But I can sort of share with you what I view as what would be the philosophical underpinning of the labeling of drugs and the way I think that they would work.

The strength of the labeling would be evidence-based so that if there is evidence to suggest that it might be a good idea that you run a genomic test or it was possible that it would be valuable, I think the labeling would reflect that it might be a good idea.

If there was compelling evidence to suggest that without the genomic test -- an example -- I don't know if you would call this a genomic test, but I'll call it a genomic test anyway. Herceptin, HER-2. If you really shouldn't be treating patients without the tests, then I think the labeling would be a lot stronger.

So I actually think that the people in Drugs do do this on an evidence base and they do try and factor in basic safety and effectiveness, and I bet that will drive it. That may not help you with a particular example, and you may disagree, in fact, with how you rate safety and effectiveness. Anybody who has looked at the re-labeling knows that they have not been particularly zealous. They've actually been quite conservative and cautious about re-labeling.

DR. WINN-DEEN: Do you have a sense that there is any drive within the agency where there is an evidence base to create some kind of guidance for who should develop, say, dosing recommendations? If you have a nominal dose for the general populace, if you're a slow metabolizer or a fast metabolizer, how do you deal with that? Is that the pharmaceutical drug manufacturer's responsibility? How is the FDA going to manage that?

DR. GUTMAN: Well, I mean, it's a huge task. We're the group that brought you CYP450, and just working through that will be a lifetime. I'll be dead before that's resolved.

But I think the agency probably doesn't have a well thought-out -- we do recognize it's a problem. I think we have some ownership in it. But I think it's certainly too much of a task for us to do. I don't know that there's an expectation explicitly that companies start doing outcome studies to do that. I think as intense as drug reviews are, I'm just not sure that we're prepared to ask drug companies to start doing that. So I think the hope is that perhaps some work will be initiated through the critical path and some work will be by companies and some work will be by academics.

One of the problems is people are always talking about the critical path and the financial and the

regulatory and the clinical use, how dumb the doctors are, but actually part of it also is how tough the science is. I may be wrong, and I may be maligning my colleagues in Drugs. They're very smart, but they're not that smart.

DR. LEONARD: Well, my question was exactly Emily's. You talk about the accuracy of the testing, is it telling you the right genotype or not, but you don't talk about what you do once you have the right genotype and you know that someone is a poor metabolizer or a rapid metabolizer. There aren't dosing recommendations. I'm now heading up a Pharmacogenetic Subcommittee of our Formulary and Therapeutics Committee of New York Presbyterian Hospital and I've been searching for these guidelines. They're very hard to find. If you're going to do the pharmacogenetic test, then what does the pharmacy do? So that's a huge gap in implementing one aspect of pharmacogenetic testing.

DR. GUTMAN: Well, I was quite serious in asking for comments. So I think that's a very fair comment. Better than comments, of course, are suggestions on how either the guidance can be shored up or how the agency could help address that. So both would be welcome.

DR. LEONARD: But you've lumped together -- a pharmacogenetic test is a heritable marker. So the title of this draft guidance is a little --

DR. GUTMAN: It's perhaps too broad still, you might argue.

DR. LEONARD: Well, it applies to both, but with genetics, you've diagnosed a disease. With pharmacogenetic tests, there's no disease you've diagnosed and any pharmacogenetic test that you do, you can go on General X's website and see that CYP2C9 has a whole array of drugs that it affects. So pharmacogenetics really is different in a way than the rest of the genetic testing that you may do.

DR. GUTMAN: No. I think that's a fair and problematic critique. I can't duck that because I think that's correct.

DR. WINN-DEEN: Is it possible to consider the warfarin model, which my understanding is that the way the studies were done was they were basically look-back studies. So they let people get optimized onto what seemed to be the most effective dose of warfarin for them and they genotyped them. And they looked to see if the genotype of HER-2C9 and VCOR1 were predictive either individually or in some. The conclusion was you could actually predict where the dose should be set, based on those two genotypes.

DR. LEONARD: Well, plus age, plus --

DR. WINN-DEEN: Well, yes, okay. Plus some other things. But the test actually provided useful dose guidance. But you arrived at that dose guidance initially through look-back.

Couldn't we ask the drug manufacturers who know that their drugs are metabolized by 2D6 to do those same kind of look-back studies, just where did they end up as the most effective dose, what was the genotype, and develop guidance?

DR. GUTMAN: I actually think that's fair.

DR. EVANS: I think one of the biggest problems with that is that it's far easier to do that in the setting of VCOR where you have a really nice quantitative measure of efficacy. Right? You've got your INR and it's a number. As opposed to doing that for, say, response to SSRIs in depression, it's much more problematic.

DR. GUTMAN: But conceptually I agree it's much more problematic because the endpoints are much more -- maybe you could do measurements.

DR. WINN-DEEN: The reality is you still titrate people to dose. Right? So if you get to that dose, however you got to it with whatever clinical feedback, then you could still try and give some dosing guidance.

I think it's very frustrating for the clinical community to see all these things. They've got the drugs. They've got the test, but they don't know how to connect the two.

DR. GUTMAN: They're not sure what the hell to do, yes.

DR. WINN-DEEN: And there's no guidance from anywhere in the federal government that I can see on who's responsible for that. And that last piece of connect the dots, I think that's part of what the task force is looking for as one of our translational medicine questions. It's who's going to step up to the plate.

DR. GUTMAN: This isn't exactly my shop, but I work very closely with the people who are making these labeling changes. They are my colleagues. Would it be your view that we should either be asking for more data before we're making labeling changes, or would it be your view that we should be more conservative in making the labeling -- in other words, are we being too aggressive? Are we being premature in terms of what we're doing or asking the wrong questions?

DR. LEONARD: From a liability perspective, it's kind of disturbing to have some labeling that says, and you may want to think about doing this because these polymorphisms affect dosing. Okay. So you do the test. Then what? And if you don't do the test with that on the label, where are you? So you're kind of between a rock and a hard place.

DR. GUTMAN: Yes, I think we need to hear that. I'm not sure we've been as sensitive to that as we should. So that's very useful input.

DR. LEONARD: But as Emily was saying, looking at doses, and retrospectively determining the genotype-dosing correlation, there isn't therapeutic drug monitoring for many drugs that we give. So you don't know what the level is or what the therapeutic level should be, and you don't have any test to measure that. It's not like INR for Coumadin. So it's not so simple to do for many drugs.

DR. GUTMAN: Well, but you've to start somewhere. Right?

DR. LEONARD: Yes.

DR. EVANS: So this actually gets to the comment I was going to make which isn't so much a question for you. In looking at the translational needs and the research -- and since I'm on the task force, I

should have probably caught this before, but I don't think the most important possible issue on here is starkly enough highlighted. That is, we can recommend and we will see all kinds of pharmacogenomic tests coming out, but what is really desperately needed are prospective outcome studies. Right? Even the great stuff that's come out on VCOR and warfarin has not yet shown that it makes a difference in outcome.

So I think, in my mind, if there's one huge recommendation that we should make to the Secretary -- part of it would be in the purview of the FDA -- that is, that somehow it needs to be encouraged that there be prospective clinical outcome studies performed. Does paying attention to the genotype make a difference and efficacy and complications and cost? I think that short of that, it's really hard to argue for the strong adoption of pharmacogenomic tests unless it's so obvious, as in the case of Herceptin, that it fits like a hand in glove. So I think we need to highlight that on our recommendations.

DR. WINN-DEEN: Francis?

DR. COLLINS: So I want to strongly agree with what Jim just said. I think the Coumadin dosing example is a telling one. We do have these look-back studies. They do certainly suggest that there is a pretty good correlation between genotype and maintenance dose, but would that actually be something that in a prospective fashion would both avoid bad outcomes, which we all know happen with this particular drug at a remarkably frightening frequency, and also save costs? You can look at the data and say, yes, it looks like it probably would, but until you've done that study, I'm not sure you really know.

In fact, that is something the Heart, Lung, and Blood Institute is very actively looking into right now, is the mounting of such a study because here's a drug that's probably not going to have this study conducted by a pharmaceutical company. It's been out of patent for how many decades.

When it comes to something like the Amplichip for P450 variance, this is much messier, as you all were just saying. I mean, to mount such a prospective study in that instance, you'd have to mount 20 different studies for 20 different categories of diseases and different drugs and where you had a much less precise opportunity to assess what looks like efficacy and what looks like a side effect. So that one is really, I think, going to be a very tough issue.

Steve, can I just ask, when FDA decided to approve the Amplichip P450, what was the discussion that went on in-house about how this was actually going to find its way into clinical practice? Or was the approval basis solely on the question of is it analytically valid?

DR. GUTMAN: No. There was clinical consideration. The drug model that was used was Strattera. That may not be the best example because you have the same problem you have with warfarin, but we were cross-labeling to Strattera, which had this recognized as a piece of information that could be used, perhaps not very explicitly, but could be used in decision-making about that particular drug.

There was also the fundamental notion that in terms of toxic states and the evaluation of patients who were toxic, that this might be helpful in sorting through what was going on.

Probably the strongest literature -- we didn't look at all. There are 41,000 articles, so we didn't look at every article on the enzyme, but we did do analysis of various parts. We saw relative strength to

the literature for psychiatric neurologic diseases, but it was only relative strength. There are actually publications that do make tentative dosing recommendations, and we were anxious to get the tool out for a variety of reasons.

But we expected that there would be two things: a long transition into actually having the information that you needed -- I actually think around 20 percent of U.S. drugs are impacted by this marker. Boy, if we had asked for a study on 20 percent of the drugs, we'd certainly have job security.

(Laughter.)

DR. GUTMAN: But there was also the notion -- and I think that Roche certainly went into it with their eyes open -- that there would be a huge educational burden here because even if you had more certainty about the signal, you can't suddenly take all of these doctors across the country and suddenly they're all going to miraculously know how to -- you know, they can hardly use ProTimes, much less CYP450. I didn't say that.

(Laughter.)

DR. LEONARD: So in the update that we were given of ex officio agency activities, there's a very interesting little bullet here for NIH, which is ethical, economic, legal, and social studies of pharmacogenetics research of the National Institute for General Medical Science. And they say, obtained approval to solicit proposals to fund research on ethical, economic, legal, and social issues related to pharmacogenetics research, specifically the hurdles of translating basic research into clinical practice.

So it seems like there's already money targeted for pharmacogenetics in NIGMS. Can this be encouraged to be funding the prospective outcome studies that might be needed? I don't know whether that's ethical, economic, legal, or social, but they are talking about translating basic research into clinical practice, which is exactly what we're talking about here.

DR. COLLINS: So that's part of the pharmacogenetics network that NIGMS has been leading the effort on for some time. I don't think that particular EELSI program contemplates actually conducting clinical studies. This is to do research of a more general sort on the ethical, legal, social, and economic consequences, but not to actually conduct such studies. That's going to have to be done by the respective institutes that are interested in that particular topic, as Heart, Lung, and Blood now is with warfarin and which we hope will get underway on that basis. Given the tight budget constraints, these are complicated, expensive studies to undertake. We'll have to choose carefully which ones can be mounted at the present time.

DR. WINN-DEEN: So is there a way that we could encourage the Secretary to ask NIH to make sort of a broader use of all the different little funding pots in the various institutes within NIH to each take on the challenge maybe of one drug related to their remit or something and start to move this along?

DR. COLLINS: That's, of course, an option for this committee. Just keep in mind that you're dealing with what is probably at the present time a zero sum. So if that is going to be encouraged, something else is not going to happen. Unless you want to be really bold and suggest that this is such a high priority, that it ought to be a special initiative, and that's, of course, something I could not advise you about.

DR. WINN-DEEN: Can you just talk to the changing thinking at NIH from basic research to translational medicine? I mean, translational medicine is now a valid area to get funding, correct, through NIH?

DR. COLLINS: Not just a valid area, I think it's the highest priority area. When I sit around the institute directors' table every Thursday morning and we talk about where our emphasis needs to be in the current era, it usually focuses on this bench to bedside transition and the word "translational" echoes off the walls with great regularity. Their challenge is to figure out how to do that and how to do it in a climate where budgets are tight and translational efforts are often large clinical studies that are quite expensive.

DR. WILLARD: I was just going to point out in response to Debra's comment, the EELSI initiative you just referred to from NIGMS has not set aside money. It is simply a request for proposals because they wanted a few more applications to come in. And heaven forbid any of them should be funded. That will just knock some other proposal off the other end.

DR. LEONARD: Well, nothing is getting funded right now, if I'm correct, right?

DR. WILLARD: I think there was something in our folder that said they were hoping to get three new applications per round and hoped perhaps to fund one per round. So this is not a major initiative.

DR. LEONARD: I didn't mean to indicate it was major. It's one in this long list from NIH that we got, and it's a very long list.

DR. WINN-DEEN: Julio?

DR. LICINIO: I have a comment, just to echo what you said, which is that NIGMS has had this pharmacogenomics network which I've been part of in the past, which is a wonderful initiative, but it is one institute's effort. While some institutes have joined forces, others have not. In a sense, I hate to use the word, but it's almost like it's used as an excuse for other institutes not to do very much because they say, you know, NIGMS is already doing this. Why do we have to also do it? So I think that something touching on the importance of dedicated funding to this area would be very important to put in the report.

DR. WINN-DEEN: Julio, my impression was that that effort, at least when I was involved in it several years ago, was really aimed at the discovery side of looking for the associations, rather than the translational side. Is there any change that's happened in that remit?

DR. LICINIO: No, nothing has changed. It's the initial intent. So again, as you said, the emphasis is on the discovery of things that could (inaudible) but not necessarily applying them to clinical practice.

DR. WILLARD: I'm going to bite at the hook that Francis just said he couldn't throw on the table, which is there's a danger and an opportunity for a committee like this that everything we recommend costs money. I can't think of anything, at least in the short run, that is going to save money for the Secretary or anyone else. But if we feel this is, among the whole panoply of things we're looking at, truly one of the most important initiatives, then perhaps we should recommend that this be looked at as a special initiative which would involve special money.

Or at least we should periodically ask that question to ourselves so that we can either say yes or no. It either passes muster or it doesn't. Because otherwise, we run the risk that everything is top priority to us at the end of the day and we really haven't been very helpful. We just keep firing letters off to Secretary Leavitt and they either sit there or come back. So we at least should force ourselves to ask that question. It's either a real priority or it isn't a real priority.

DR. EVANS: I'd really agree with that, and I think that this particular subject may be more amenable to that kind of thinking than much of what we deal with. The reason I say that is that I think you could make a strong argument that some of the ELSI considerations in pharmacogenomics do not loom as large as they do for, for example, large prospective studies. When you're talking about response to drugs, you're talking about very narrow genetic information, genetic information that is applicable only in a very narrow clinical setting, that is, when you're going to use that drug.

So I don't mean to gloss over potential ELSI issues, but I think with this subject, the issue of efficacy and demonstration of efficacy prospectively looms very large, and some of the other issues might not loom as large as other subjects we deal with. So I think we should give consideration to that.

DR. WINN-DEEN: I just sort of wanted to respond to Hunt's comment, which is my job is strategic planning. I have to think about product portfolio management. So I'm going to approach this from the same way.

This is an opportunity for a near-term product that we could have that could actually make an effect on the health of the American people. Funding a long-term population study is one of those long-term investments that you make, knowing that you're not going to see any fruits from that for 10 or 20 years.

So I think part of our responsibility is also to be looking at both ends of that portfolio management and give the Secretary things that we can do today that are immediately applicable and also give him the broader view of what do you have start today to be where you want to be in the future. So from that point of view, I think this is an area where we could have a fairly near-term impact on a number of treatment decisions.

Debra?

DR. LEONARD: I agree with Hunt, Jim, and you. I think that this is an area that could warrant this extra funding, special initiative, or whatever it's called.

I don't think we've been spending a lot of money. If you look at the FDA-FTC interactions, we fostered that. The genetic nondiscrimination legislation we're promoting. The large population thing, we don't even know whether we're promoting that or not. But I don't really think that we're spending money left and right, and I think this has the great potential for significantly affecting the health care of a lot of people quickly or over the short term.

DR. WINN-DEEN: James?

DR. EVANS: One other comment for the FDA. I don't understand how the FDA works.

DR. GUTMAN: Well, I work there and I don't either.

(Laughter.)

DR. EVANS: But I would just make a plea for the idea we're talking about the fact that these things cost money and the public sector only has so much, as does the private sector. But it does make sense to me that the FDA, at least when applicable, if companies want to use the power of pharmacogenomics to help guidance, then it certainly seems reasonable to try to shift some of this burden onto those people who develop and make the drugs and makes claims for them. So I would just say that it is reasonable, whenever we can, to try to ask for, again, the right kind of studies, studies that show clinical outcome efficacy.

DR. GUTMAN: Yes. I actually think the problem here is one of hierarchy. I actually think that for a new drug that had tests associated with its safety and effectiveness profile, that would be easy. I think it's harder for something that's 30 years into use and that's generic. But I actually think that that is easy for new products. It's the retrospective fit that's a little more challenging.

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

DR. RANDHAWA: Yes. Picking up on the thread that we need to consider prospective observational studies or even randomized trials to try and get at the efficacy of new drugs and the interaction with genes, and also picking up on the thread that we are in an era of limited resources and considering how many drugs get developed and how many genes are in the human genome and how many permutations and combinations we have, it is not feasible to mount observational studies de novo.

I wonder if the committee would like to discuss strengthening and improving our ongoing hospital-based data collection systems and, further, to try and get at a sense of what genes and drugs and for what conditions can we be relatively satisfied by database mining analysis studies and for what genes and conditions and drugs would we need to mount large, new studies. That might be a solution to this discussion.

DR. BRADLEY: Yes. We've been spending a lot of time talking about the need for these practical clinical trials at CDC as well, and of course, one of the reasons for that is that we fully realize that one of the things that EGAPP is going to do is going to be to lay out lots of gaps in the information that we have.

So one of the goals that the working group has in making their recommendations on specific topics -- two of the topics that we're dealing with, obviously, are pharmacogenomics -- is to lay out what are the key research questions. One of the things that we really hope to be able to do, in collaboration with other groups, is to use systems that already exist, for instance, the HMO research network, and other such groups, to be able to both give the reasoning for why we need to do these practical clinical trials and find some money to support them.

DR. WINN-DEEN: Can you just remind us what the two PGX projects are?

DR. BRADLEY: Yes. CYP450 in depression. We took on the big ones and SSRIs and UGT1A1 in colorectal cancer and irinotecan.

DR. WINN-DEEN: So that's even in the presence of a test and labeling on irinotecan. You're still going to go ahead with that.

DR. BRADLEY: Well, we're going to be looking a lot at outcomes, obviously, clinical validity questions, and how do you change that into dosage recommendations, and what are the outcomes.

DR. WINN-DEEN: Other comments? Debra?

DR. LEONARD: Steve, at what point does the FDA move from saying -- so, when a drug comes to the FDA, they have to have dosing specifications. Right? They'll say you start a person on this dose. At what point does the FDA start moving toward you have to know how the drug is metabolized and for someone of this genotype, you have to give dosing; that genotype, you have to give recommended starting dosing, et cetera?

DR. GUTMAN: Well, again, it's within space. So it depends on what is either known generally or what's known specifically in the submission that the drug company makes.

DR. LEONARD: But if the FDA requires that, then the drug companies will do it, and if they don't, they won't necessarily.

DR. GUTMAN: FDA regulations I think are more flexible than perhaps is generally appreciated. The voluntary genomic data submission, this safe harbor, is actually not entirely safe because if the FDA does -- it's a sharp sword. The FDA is very concerned. My colleagues are very passionate about their public health mission. If they become familiar with pharmacogenomic data that they suddenly think is critical in the life of the product, it no longer is voluntary. It does, in fact, leap-frog into something that we would probably hold the product hostage to.

So it's very interesting. I was at a meeting at the Institute of Medicine last week, and there was a lot of discussion about biomarker studies. Rick Simon from NIH, who makes an avocation or actually a lifetime devotion to nothing but statistical design for this kind of stuff, was pointing out that if you do something as daring as study the entire population and study the biomarker at the same time that you're doing a drug treatment, you have two things you'll see at the end of the study. You'll have the drug effect in the untested population and you'll have the drug effect in the tested population. And he raised two issues.

One is that if at first you don't succeed and you try, try again, if you first look at the whole population and then you look at the subpopulation, you have to pay a statistical penalty for that. He actually had models on that penalty.

Then he made the second, I think, startling -- to me, almost an epiphany, which is that if you look at the entire population and the drug works, you wouldn't have to unblind and look at the subtested population. There's nothing in the law that says you have to do it. There's nothing in the business plan that says you have to do it. It might be a very nice scientific gesture to do it. And there's the potential that the overall impact in the whole population is actually not a total population impact. It's being driven by the power of the drug only in the marker-positive.

So it would be his view that the scientifically and public health responsible thing to do, whenever

you do that kind of study, is to unblind the marker so you can make sure that even if you have this blockbuster drug, it's not a blockbuster because of the power in the subpopulation.

There was a very candid manufacturer, a very candid drug company in the audience who says, well, that's great. That's not part of my business plan. As soon as I show it works in the total population, boy, I'm not going to waste money doing a biomarker study.

So you have to realize there are some limitations. Regulation isn't perfect.

DR. WINN-DEEN: James?

DR. EVANS: And beyond that, what the drug companies worry about is they don't want to demonstrate that only 40 percent of the potential market is going to respond.

DR. GUTMAN: I think that that's absolutely true. But I actually see not a quantum but a definite evolution in the sophistication of the drug companies in terms of their appreciation that there's something in this for them, and what's in it for them is that they really might have more than a 10 percent success rate. They might double it. There's real money there. What's in it for them is they might have to look less often for bailouts or they might have a bailout.

I know that the diagnostic industry has complained, and perhaps rightfully so, about value-based reimbursement, but I actually think that there are some companies, big companies, small, that are starting to get the fact that there might be a payoff for not necessarily going after the blockbuster drug. And I just don't know that that's a universal construct. I don't know if everybody has bought it, and I actually don't know if it's true. But I think that people are acting like it might be true.

DR. WINN-DEEN: Any more general comments before we go on to a sort of specific discussion?

(No response.)

DR. WINN-DEEN: Let me just ask you, Sarah, a point of order. Could we break earlier and then have the more general discussion? I'm concerned that right after the break, we're supposed to have public comments. So should we go another 15 minutes?

MS. CARR: There's one public comment scheduled for today I think. So I think we can break now. Did you want to?

DR. WINN-DEEN: I think we had our general discussion and I'd like to come back after the break and start the specific, let's walk through the report. It seems like a more logical time to break, if we can do that.

MS. CARR: Sure.

DR. TUCKSON: You have the power of the chair. You can do whatever you want.

DR. WINN-DEEN: Yes, but I don't control our Internet transmission.

DR. TUCKSON: So you want public comment and then break?

DR. WINN-DEEN: We can do that if we can get the public comment.

MS. CARR: Is Gail Javitt here? Do you mind doing it now, Gail?

MS. JAVITT: I'll speak fast.

DR. TUCKSON: No, no. You don't have to speak faster because we want to hear you. So we'll hear the public comment. We'll take the break, and then we're going to come in and roll up our sleeves and drill deep at the 100th power of the microscope.

Thank you and welcome. Please introduce yourself for the record, and we're glad that you came to speak to us.

MS. JAVITT: Thank you. My name is Gail Javitt, and I am Law and Policy Director with the Genetics and Public Policy Center at Johns Hopkins University. I appreciate the opportunity to appear here today and to speak to you about the center's concerns with respect to engagement testing quality and pharmacogenetics.

As this committee has recognized, pharmacogenetics holds great promise to improve the public's health by improving the safety and effectiveness of pharmaceuticals.

But the success of pharmacogenetics is predicated on a robust pipeline of genetic tests, and these tests need to accurately and reliably detect variations in DNA. This means, in turn, that the laboratories that do the testing need to have the capability to perform these tests accurately and reliably, that the tests themselves provide clinically valid information, and that health care providers, as this committee has discussed, know how to interpret the results.

We are concerned that the current regulation of genetic testing is shaky and is not strong enough to support the foundation on which pharmacogenetics is based. Although the public widely believes that the government regulates the quality of genetic tests, for the most part this is not the case.

First, today there is no specialty area for genetic testing laboratories under the Clinical Laboratory Improvement Amendments of 1988, or CLIA, as it is better known. This situation exists despite the fact that this committee's predecessor, the SACGT, recommended the development of such a specialty, that the CLIAC developed a proposal for such a specialty, and that CMS indicated in 2000 that it intended to create such a specialty.

So we at the center were curious about why there might be such a delay of six years. We wondered whether perhaps the comments that were submitted in response to the notice of intent of 2000 were overwhelmingly negative, leaving the agency to perhaps change its mind. So we undertook a thorough review of those comments, but instead of overwhelming opposition, we actually found significant support for the creation of a specialty, although there were differences of opinion about the details. But on the issue of proficiency testing, which we believe is the central element of ensuring the accuracy and reliability of testing, there actually was consensus that a specialty should be created.

So based on our analysis, in November of 2005, we sent a white paper to CMS Administrator Mark McClellan, along with a letter urging him to issue a proposed regulation for a genetic testing specialty under CLIA, and subsequently the Genetic Alliance sent a similar letter.

So turning, second, to the genetic tests themselves, there are gaps in oversight here as well. Today there are two paths by which a genetic test can come to market and be offered to the public. Genetic testing laboratories, in performing genetic tests, can use a so-called test kit or they can make the test themselves in-house. The vast majority of tests are performing using in-house technologies.

As you've already heard, if a laboratory uses a test kit, the manufacturer of that kit must first obtain approval from FDA, and FDA assesses both the analytical and the clinical validity of that test kit, ensures that the labeling is adequate, that the claims made are supported by the data, and that post-market surveillance is done, and any adverse events associated with the kit are reported.

In contrast, if a laboratory uses an in-house test, there is no pre-market review of that test. Some components of the test may have to conform to FDA labeling and good manufacturing practice requirements, but there's no expert body to review the test and ensure that it actually detects what it purports to detect, and that the mutations detected are clinically relevant.

So not surprisingly, of the more than 900 genetic tests that are available today, a very small handful are actually sold as test kits, and an even smaller handful of the handful relate to pharmacogenetics. To compound the regulatory inequity, even once a test kit is approved for a particular indication, a laboratory can offer its own proprietary test for the same indication and this actually is already happening in the case of pharmacogenetic tests.

As we've heard, FDA has, in the past few years, recognized the potential value of pharmacogenetics, and its guidance documents indicate that the agency intends to regulate pharmacogenetic tests, although the precise framework is still evolving. But these diligent efforts will be undermined unless FDA's requirements apply to all pharmacogenetic tests regardless of where they are produced.

The absence of adequate oversight also means that physicians and the public are hard-pressed to distinguish the good performers, the good tests, from the bad tests, and they have little assurance that the tests they're using to make profound health care decisions are reliable and relevant predictors of disease risk or treatment outcome.

So if pharmacogenetics is to gain the public's trust and, equally important, the trust of payers, and to deliver on its promise of health care improvement, there must be a sufficient level of confidence that the laboratories offering the tests are performing them correctly and that the tests yield information that is relevant to health care decision-making.

Getting to the system that is worthy of public trust will require the Department of Health and Human Services to give the necessary direction to the agencies that are involved in overseeing both the laboratories and the tests and to implement needed changes.

So we would encourage this committee to make a recommendation to the Secretary that CMS issue a proposed regulation for a genetic testing specialty under CLIA, and we would also encourage this

committee to recommend to the Secretary that a regulatory framework be established for genetic tests to ensure that they are clinically valid, regardless of whether they are performed using a test kit or an in-house developed method.

And I appreciate your time. Thank you.

DR. TUCKSON: Well, thank you very much.

Let me just ask. Again, we're pretty bright, but does anybody have any questions they want to ask?

I was trying to allude to the fact that I wanted to revisit some of the strategic planning priorities at the end of the session tomorrow, and I know that there are going to be some of us around the table who feel strongly about maybe not revisiting the oversight question because, Lord knows, it's complex. But this issue generically first is something that is on my mind about do we really need to make sure we're clear about where the holes are between CLIA and FDA and FTC and others. You know how we resolved all the home brew. This has been worrying me in terms of our responsibility to the Secretary in terms of continuing to make sure that we're clear on if there are holes, and if there are, either we accept those holes or don't worry about them.

So, anyway, I'm telegraphing that this is something that I'm concerned about. I don't want to live with the anxiety as the chair about this a lot longer, so I'm going to dissipate my anxiety into each of you.

Here we've got that same issue being raised, as well as the specific issue of the notion of a special discipline that you're advocating for. So I'm going to come back to this tomorrow.

By the way, I'm giving fair warning to the committee to kibitz me at the break or anywhere else if you want to try to tackle me and prohibit me from going down roads that you really don't want me to go down tomorrow. So I'm giving you a chance.

But meanwhile, are there any questions that you want to ask specifically of this report before we get to that larger discussion tomorrow?

DR. LEONARD: I'd just like to lend support. It would be great if CLIA could come out with their genetic CLIA recommendations or subsection. It's been missing in action for I don't know how long.

DR. TUCKSON: Exactly. Right.

DR. LEONARD: But I ask all the time, and it's coming, it's coming, it's coming is all I hear, but it never appears. So can we put this on the agenda to get an update and explanation as to why it's missing in action for so long?

DR. TUCKSON: This is where I'm coming from. So could you make sure, knowing that I have a memory like a bowl of jello here? This is what we want to revisit. Would you write down that particular recommendation? We'll do that tomorrow. Terrific. That's just what I'm getting at.

Are you guys good. I pulled out of my notes that were just handed to me. CMS says genetic

testing specialty under CLIA rules, forthcoming.

PARTICIPANT: What's the date on that?

DR. TUCKSON: Now, first of all, I'm not going to do that to CMS. I'm just letting you know. We like CMS. We're not going to mess with them. Besides, people report on everything we say. It comes back to haunt you. So we'll give them a chance to respond.

Anything else on the recommendation, which is actually an interesting one? Do we have it in writing yet?

MS. JAVITT: I'll be happy to submit it in writing.

DR. TUCKSON: That's a good answer.

One was the CLIA and one was the --

DR. LEONARD: Right, and the other one, CAP has gone to including the review -- there's a specific now review in their checklist. So every two years, any new tests that are brought on-line need to be reviewed during that review process. But that's not part of CLIA. So if that were addressed under CLIA, then it would become more generally applicable for anyone doing inspections of laboratories. So that's one way that that second oversight of non-FDA-approved or reviewed test kits or genetic tests done using non-FDA-approved or reviewed test --

DR. TUCKSON: So we'll bring that up again tomorrow. Did you get that second one? If not, get with Debra. That was perfect.

All right. You're going to submit that in writing so we'll have it?

MS. JAVITT: Yes.

DR. TUCKSON: Thank you.

By the way, is Marilyn Zigmund-Luke around? You might have wanted to testify?

MS. ZIGMUND-LUKE: I'll talk tomorrow.

DR. TUCKSON: Okay. We'll get you when you do come tomorrow.

Thank you. Good job.

A 5-minute break.

(Recess.)

DR. TUCKSON: Behind schedule. Shame on us.

Well, what I'm really concerned about is that Emily is going to have to wind up having to chair

the last half hour of the meeting because I've got to be someplace to give some kind of major keynote. I'm trying to be the bad cop so Emily doesn't have to be at the end. So I'm saving her again, so you'll think she's the most wonderful person and I'm the bad person. So that's the way it works.

All right. We're going to go ahead and roll up our sleeves and drill deep and let's see what happens.

DR. WINN-DEEN: Turn to page 1 of your yellow pages, entitled "Background Information on Proposed Approaches."

PARTICIPANT: This is the second page 1?

DR. WINN-DEEN: Yes. The other page 1 has some other title on it. I just think it's useful to have all the stuff together in one place.

So we clearly already had quite a bit of lively discussion about translational needs. So I don't know that we have to reiterate that except to say that there are things going on, but I think from the sense of the committee that maybe we don't think there are enough things going on or that there are still some gaps in the translation process.

So we had introduced a couple questions in this section. Do the current research activities meet the needs identified by SACGHS, and how should research to determine the effectiveness of pharmacogenomic-based drugs and tests be conducted, especially in a diverse population?

We had, under proposed approaches, that we should promote inclusion of diverse populations in pharmacogenomic studies and that potentially health care organizations could become more actively involved. I think what I heard from the discussion before the break was that there's a more fundamental gap there which is that we really need to be funding the final phase of translational research. So once we understand that there is a genotype that could be associated with a drug response or affecting drug dose, that we need to take it to the next step, which is to actually develop the data set, which drives the clinical practice on drug dosing and economics.

So I'd like to add another potential recommendation in there, as well as opening the floor up for discussion on the two recommendations that are up on the screen right now on making sure that we include sufficient diversity and that we also try and reach out to the private sector to the health care organizations that may also have quite a big database of patients and outcomes that could be partnered with to develop the translational information that we need.

Let's take comments and questions. Debra?

DR. LEONARD: So, Steve, does the FDA even require pharmacogenomic studies? They don't. So in this first recommendation, I'm not quite sure what we're stating. You've got this friendly agreement they have to kind of provide it to you and there's a safe zone unless they find something. Then it's not safe anymore.

DR. GUTMAN: It's a matter of the state of knowledge. So if it's a valid biomarker that in some way has been linked to a product, I don't think you get to duck it. It's a question of how much due

diligence and discovery might be required. But if there are known associations that impact the safety and effectiveness, then they become part of the review process.

DR. WINN-DEEN: Can I ask a follow-up on that? Isn't most of the diversity mandated by trying to make sure that the drug is tested during clinical trials in the total type of population that it would be used for? Isn't that really where it's mandated?

DR. GUTMAN: I'm not credibly familiar with all the nuances of drug review, but I know they, like us, have been asked to be more inclusive, to worry about gender issues, to worry about pediatric issues, to think about representative populations. So whether we're doing as well as we could, I can't say, but I know that certainly is part of our psyche to worry about things like that.

I think this is particularly unique because you do see very striking sort of population-specific differences that we might historically -- certainly in my shop we've not historically looked with quite the refinement that this might call for, and I suspect that the same might true in Drugs.

DR. WINN-DEEN: Did you want to say something else, Debra?

DR. LEONARD: Well, I don't know if this first recommendation or proposed approach makes sense.

DR. GUTMAN: Well, it does to the extent that --

DR. LEONARD: Yes, we want diverse populations included, but I'm not even sure the FDA is requiring pharmacogenetic studies to begin with to promote the diverse populations.

DR. GUTMAN: But if we weren't requiring them but a company came along with them and said that they want them because they'll help make the product more safe and effective or they'll help avoid toxicity or they'll help direct therapy, whether they're required or not, they are sometimes and they're likely more often to come along. So it strikes me that this is a matter of degree, not whether you should include diverse populations. This seems to me a safe recommendation, and it will apply to some products. It may not apply to all products because of the variable nature of what FDA might see or might request, but that doesn't mean this is an invalid request.

DR. WINN-DEEN: Yes. So should we just maybe word it a little differently so that we have the caveat when pharmacogenomic data is being utilized as part of a drug review, it should be gathered from a diverse population or a population reflective of the population that would be taking the drug?

DR. GUTMAN: If you have a more fundamental fault with the process, then you should say, and in addition, we think you should always look at pharmacogenomic data. But for when we do look at it, in those instances, it's just a no-brainer we should be looking at diverse populations.

DR. LEONARD: Well, recommending looking at pharmacogenomic data -- Sarah and I were having a conversation at the break that pharmacogenetics means several different things. One is it's getting the right drug for the right variant that's associated with disease, like Herceptin and HER-2/neu. You don't give Herceptin if there's not HER-2/neu amplification. The other is getting the right dose of a drug that will be effective, but you want to get to therapeutic and not to toxic levels.

That's a limited set of metabolic enzymes, transporters. We know most of the metabolic pathways by which drugs are metabolized, taken up, excreted. So in that case, you could ask every drug submission to say how is this drug metabolized, what are the variants, and do you have dosing recommendations. Sometimes with drugs, you don't know the genetic variants that they should be targeting, so you can't ask for that all the time. But the dosing area is fairly straightforward, I would think, unless they can submit data saying that we haven't been able to determine this or we can't or it's not metabolized by the regular pathways, or whatever.

DR. GUTMAN: Yes. I apologize I'm not more expert in drug either process, procedures, science, or regs. But my sense is that none of this would be alien to drug reviewers. I actually think these would be questions they would be quite interested in asking, and they probably would ask to whatever extent they thought was appropriate. So what you're asking for is something that we either already probably ask for or it certainly strikes me as things we should be asking for, perhaps with increased vigilance as this field emerges.

DR. WINN-DEEN: Gurvaneet and then Cindy.

DR. RANDHAWA: We have got a couple of issues here. One, I'm not quite sure if it's that simple to get into a straightforward dosing algorithm based upon whatever variant, metabolizer, or transport or genotype we have. If you look at what condition the drug is being used for, and there are other pharmaceutical agents being given, drug interactions become an issue, perhaps a major issue, which may not be there in the drug trials to begin with. So I think there has to be a caution as to how much specificity FDA can give in its labeling advice for drug and genotypes.

The second issue I just want to clarify is here it says diverse populations without specifying what diverse populations mean. To me, genetic diversity is not the same as what Steve had mentioned about elderly population, younger population, and even the way risk is defined, it's more geographic inheritance rather than genetic inheritance. So can we have a little bit of precision of that?

DR. WINN-DEEN: It seems to me that if we're talking about genetic testing, it should be genetically diverse rather than age diverse. I think we could probably add that clarification.

MS. BERRY: I was wondering if there was something that we could put in a recommendation -- or maybe the group had already thought of this and rejected it -- that would go a step further and either provide an incentive for companies to conduct these types of analyses and provide this kind of data. I mean, you can do the hammer approach or the carrot approach, and there are pros and cons to each. If we feel that there isn't enough of that back-and-forth and submission of data, is there something more we would like to propose, or do we think the status quo is okay?

DR. WINN-DEEN: Yes. I guess part of what we still don't have -- I think the drug manufacturers would like clarity for how to design their clinical trials because this is a long process. It's probably a year in design and then two or three years in execution and another year in review and comment from FDA. So the better you can do the design up front, the less issues there are to discuss with FDA on the other end.

So I clearly think that the FDA can play a leadership role in helping to guide the way trials are designed. So I think that's our opportunity through HHS to really influence it. We don't control big

pharma or little pharma. For that matter, we don't control private industry, but we can influence the way things are done to provide better medical outcomes.

I think FDA has been working to have two different categories: the "validated" biomarkers where, if you know that your drug is involved with one of these validated biomarkers, you're supposed to include it in the trial, period; and the exploratory research that might lead to discovery of a new biomarker, and that's part of this voluntary data submission. They've been really actively encouraging companies to do both kinds of studies, not just the mandated ones, but also the "maybe we'll find something" kind of studies.

I don't know what else we can do through HHS to encourage that. If people have other suggestions, I'd be happy to hear them and consider putting in some recommendations.

DR. LEONARD: I very much like Steve, but I'm wondering if we don't need someone from FDA Drugs because Steve is basically from SACGT and the carryover of the oversight issue and everything. The testing is one aspect. I'm not saying get rid of Steve. I'd like to keep him. But maybe we need someone from FDA drug review, I mean, Steve's equivalent on the drug side.

DR. WINN-DEEN: We've had Felix here.

DR. GUTMAN: I'm certain you can find someone either to join or to attend as appropriate. They're not trying to hide. Maybe they are. No, I don't think they're trying to hide. I think they would actually probably have found this discussion interesting.

DR. TUCKSON: Do we generally put ex officios on any of the subgroups?

MS. CARR: Yes. There are a couple people from Drugs on task force.

DR. TUCKSON: So we can informally ask Steve, would you please be the conduit and say that we would like on this subcommittee the right person from FDA other than you?

DR. GUTMAN: Yes.

DR. TUCKSON: That's just a formal deal which we will transmit formally. Thank you.

DR. WINN-DEEN: Joe?

DR. TELFAIR: I have both a question and (inaudible) on the answer. But it's a little bit different than the current thread. It's for number 2. It has to do with number 2. If we're ready to move there, just let me know.

DR. WINN-DEEN: Is anybody else commenting on number 1, or are we ready to move on?

(No response.)

DR. WINN-DEEN: All right. You're on, Joe.

DR. TELFAIR: Okay, thank you.

The idea of diverse populations was clarified. I wonder if we can also clarify health care organizations. Is there already a list of ones that most people would recommend, or is it something that we really need to be clear about, given the thrust of this recommendation?

DR. WINN-DEEN: I think what we were thinking when we wrote that was to involve folks outside of HHS like a Kaiser Permanente that's a big health care organization that manages lots of patients, has lots of data. They actually have done a bunch of studies on utilization of genetic tests and what makes sense in their practice. So those kind of organizations I think is what we meant when we wrote this.

Do want us just to say private health care organizations?

DR. TELFAIR: Just operationalize what you mean. I think that would be really helpful in order to be able to better understand what the recommendation is about.

DR. LEONARD: Also, we can only make recommendations to Secretary Leavitt.

DR. WINN-DEEN: I think we were trying to foster public/private partnerships.

DR. LEONARD: Well, but maybe we need to recommend to the Secretary that he could involve and explore mechanisms for encouraging or involving, but I don't think we can ask health care organizations to become actively involved.

DR. TELFAIR: That was it. Thank you.

DR. RANDHAWA: Perhaps you have another recommendation coming, so this may be premature. But regarding active involvement of health care organizations, they're already collecting data routinely. It's mainly claims data to pay bills. But all health care organizations want to get paid, so they do collect data, which is accessible to researchers.

One of the issues that we really have is genetic tests in particular, but lab tests as a whole are not really well represented in the claims databases. So what we are lacking more of is an infrastructure modification rather than the lack of ability or interest from health care organizations to capture the data.

So I don't know if you were thinking of having a separate recommendation on improved infrastructure or data infrastructure which then can have data available for researchers, or is it going to be a separate activity of health care organizations actively doing prospective studies independent of routine data collection?

DR. TUCKSON: Well, two comments.

One, let me, just as I answer that, revisit something that we just heard in terms of responding to Joe's point. It is true, Joe, that our recommendations are to the Secretary. I do think that we have taken the opportunity on more than one occasion to raise issues that are within the public domain that we would sort of think are important. So it is that we could legitimately say in the body of the report, while

recognizing that the Secretary doesn't have control over it, the committee is interested and would be hopeful that a certain constituency reading this report might be stimulated or motivated to voluntary action on their own. So you can get that in. I wanted to make sure that everybody continues, even though we are being disciplined about recommendations. We are talking to the American people and you can do that.

One thing in terms of your comment is that you may find fertile ground in this then in being able to link this to the Secretary's issues on health information technology. There is a lot going on in terms of collecting and synergizing laboratory data with claims-based data in a more interactively dynamic way. Without getting into the granularity of that, there's a lot there. Companies like ours do that and many others are. So the idea of a common data platform that would allow that activity to be able to be a foundation for this kind of activity would be something that would be in the Secretary's domain.

DR. WINN-DEEN: It's my understanding that the CMS codes for tests allow you to report a test for reimbursement under certain codes that reflects what that test was, so that we should have some kind of database of what the testing that's actually going on is. It's not just lab tests without any further description.

MS. AU: I think it's on page 4 under infrastructure, the electronic medical record, collecting the data. That I think you put in the recommendation already. It's under infrastructure, point number 4, middle of the page down. So it is there.

DR. WINN-DEEN: Right. One of the things that I know that has been happening within the CMS coding for molecular genetic tests is going away from just having a procedure code that says sample preparation or whatever to having a little dash after that that indicates the actual test. What was the sample prepared for? What the test was? So in the past, it was difficult to track which tests were which, but we should be able to do that now more properly going forward.

Did you want to comment, James?

DR. ROLLINS: Yes, I'll make a quick comment on that. It is true that laboratory testing is something that CMS is trying to get a better handle on, but if that laboratory test was performed in a hospital and it was part of a DRG, it may be difficult to capture that. Tests done outside the hospital are more accessible.

DR. WINN-DEEN: Okay. Because it's just billed under the DRG and that's, I suppose, too even for private insurance. Is it not, Reed, that under DRGs, all the stuff that's done is just under there and you don't really see the granularity?

DR. TUCKSON: Right. That's the challenge.

DR. WINN-DEEN: All right. So maybe there's some infrastructure that can be built somehow even for DRG-related things.

More comments about translational needs? I think that we came up with some comments, in addition to these two, about wanting to encourage the funding of translational studies through NIH funding mechanisms. So I'd like to add that. We discussed that previously. We'll get some better

wordsmithing than what I just said. Whether we should go to the encourage special additional incremental funding or just to encourage that each of the institutes within NIH should strongly encourage their groups that are developing the RFPs to consider making sure that there's translational medicine going on in all of those areas and not just leave it to PharmGKB or the National Institute of Medicine to do things, that each institute should be looking at it within what disease areas they are responsible for.

DR. TUCKSON: Well, I think I'm influenced by something that Francis said, and I want to make sure I understand how to do that. The idea of translational, as you said, bounces off the walls there. I'm saying this for debate not because I think I know the answer.

I think I'm a little concerned about if we were to recommend new funding streams because I don't think there's much practicality there. We barely got any money in the NIH as it is.

But I think that if we could find a way to sort of say that within the prioritization of the use of resources at NIH, we're saying this is important, we think it makes sense, and that within that, we think that such and so and so should occur. Can you help me with that?

DR. WINN-DEEN: Well, I guess I agree with that, that I don't think we should go back to Congress and say, you must give us X millions of dollars for this particular purpose.

My concern is I don't want to see other agencies within NIH saying, someone else is taking care of that, because this really crosses all the borders. So I'd like to see each agency charged with looking within their purview, within their things that they have to do in translational medicine -- and I assume that all of them have a charge to be doing something -- that they should consider pharmacogenetic things as appropriate for funding in their translational medicine component.

Does that seem like a rationale way to do it? Because I'm afraid that what will happen, Francis, is that everybody will say, well, that genetic stuff, that's Francis' job, and it will all have to come out of one or two agencies rather than being spread across all of them.

DR. TUCKSON: Good point.

DR. COLLINS: So I think if you're going to make such a recommendation, it would be good to be very explicit about what kind of studies you're talking about. Translational, of course, covers a vast array of applications. Pharmacogenetics covers a reasonably vast array.

What I heard people saying earlier was you would like to see more effort in prospective trials of pharmacogenetics to see whether those are, in fact, cost effective and avoid toxicities and failures to respond to drugs that are already on the market because I think we heard earlier that the drugs that are in development, this is hardly what NIH is going to be doing, this is what the companies are going to be doing. So if you could be fairly narrow in the definition, I think that would help people understand your intent.

DR. WINN-DEEN: Do you think it's a good idea to try and encourage all of the institutes to have a look at this and at least start considering it and incorporating it? This is, from my way of thinking, a little bit in our mandate to teach others to not think that genetics is this exceptional thing, that it needs to be just pigeon-holed in one or two places.

DR. COLLINS: I think many of the institutes, maybe not all, are already thinking about this and looking for research opportunities. I don't think pharmacogenetics is either sort of relegated to one or two support systems or considered to be really esoteric stuff. But this, undoubtedly, would make an impact if this were perceived as being a very high priority.

Again, I'll just remind you that unless you're going to ask for a special appropriation, by saying this is a high priority, you're saying something else is not.

DR. WINN-DEEN: I mean, each institute has to decide on their own --

DR. COLLINS: They do.

DR. WINN-DEEN: -- what that relative list is. You do that every year anyway. Right?

DR. COLLINS: We do.

DR. WINN-DEEN: Comments?

(No response.)

DR. WINN-DEEN: I'd like to move on to the regulatory issues. So we've gone through a number of these things particularly in our discussion after Steve's talk today.

We had identified specific needs of wanting to see better coordination between the research and the regulation. I think the pharmacogenomics data submission is a really good step in trying to coordinate that and make it less scary for pharma companies to actually do the research. Obviously, that also helps with incorporation of pharmacogenomics into the early stages of clinical trials.

Number 3, guidance is needed on how and when pharmacogenomics will change labeling practices. That seems to me to be the biggest gap today in terms of both pharma companies and their potential partner companion diagnostic companies really understanding what the process is within FDA to look at some data, look at a drug and change the label.

So I would like to ask that at some point FDA consider publishing a guidance or an informational kind of white paper that would just help those of us that haven't done it and even probably some of the people who have done it really understand what the FDA is thinking about, what are the criteria that they use. Is it only severe adverse events? Is it optimization of response? What are the criteria that would cause you to put something in a label and at what point does a test have to be, I'll call it, commercially available either through a reference lab or through a diagnostic kit. Are there some criteria or some circumstances under which a reference lab test is not suitable, where it has to be an FDA-approved test? So to just provide some information on those things back to the community. That to me seems like it's still a gap where we could ask for more information.

Are there other things that people are concerned about? We have this one that's up here that was something that we had also talked about within the committee. Again, this would be helpful in that whole labeling thing. At what level do you say that you need testing? If it's a 1 in 1,000, you need a test. If it's 1 in a million, you don't. You can live with the risk. So I think this question that's up here is a subset of

that whole discussion of how and when do you get a test incorporated into a label.

Are there more things that people would like to see in this regard?

DR. LICINIO: The adverse reactions I know go into two major groups, the kind of common and not so severe ones that, you know, it's nice if you can avoid them, but you know nobody is going to die of them. But the most troublesome are these that are really severe, this kind of idiosyncratic reactions, anaphylaxis, the Stevens-Johnson syndrome, and things like. They tend to be very rare because otherwise the drug will not be approved.

So to get enough cases to do a meaningful study, you really have to foster like a national registry or national collaboration because not any one center can do it. The way that research is funded now, you have to apply for your own grant to do your own thing. But I think that if some comment could be made about maybe creating like a national registry or database for severe reactions that then could be the --

DR. WINN-DEEN: Is there not already an adverse drug --

DR. TUCKSON: There actually is one, yes. Steve, you may not know everything in the FDA, but there is a new effort, isn't there, to create a registry?

DR. GUTMAN: Yes. Well, there's actually always been a program called MedWatch and there's always been both an obligation and a voluntary reporting mechanism there. There's reorganization in the Center for Drugs to provide more independence to the group that is looking at adverse drug events, and there is some change in resourcing and systems. So the agency actually has taken its notoriety very much to heart and is trying.

Actually there are some corollary things going on in my own Center for Devices that are following suit trying to --

DR. LICINIO: But just a question. In this case, the different people, let's say, from different parts of the country report to you, but they're not in touch with each other. They don't know who the others are. So there is not like a real kind of a network that the people who had the reactions --

DR. GUTMAN: Yes, that's correct. There's not a listserv or an information sharing pool.

DR. WINN-DEEN: So it sounds to me like what we need is sort of a follow-up mechanism or a loop-back so when MedWatch identifies something that there is then a way to immediately get out and study those people?

DR. GUTMAN: Oh, no. You may argue that it could be more effective or different, but that exists now.

DR. WINN-DEEN: So there's a way right now through MedWatch to go out and get a genetic sample, for example, from each of the people who had an adverse reaction?

DR. GUTMAN: That I don't know, but there's a mechanism for doing all kinds of things, including contacting companies, contacting hospitals, contacting laboratories, directing inspections. I

don't know about collecting and running samples. I would think that that certainly is within the purview. It might be challenging operationally.

I think that the regulations are strong enough to allow a fair amount of flexibility. So the question is making them operational for an event like that.

DR. WINN-DEEN: Francis?

DR. COLLINS: So the AERS database is a potentially valuable source of cases of this sort, but it certainly is not an easy or uniform solution, given that it is voluntary.

DR. GUTMAN: No, no.

DR. COLLINS: Well, okay. What percentage of adverse drug events are actually reported?

DR. GUTMAN: Now you've got me.

DR. COLLINS: I think estimates are maybe 10 percent. So it's not capturing a lot of what happens.

While it is possible, I know from talking with folks at FDA about this, to get back to the individual who suffered the reaction and try to get a sample, it's not straightforward. You have to work through the reporting physician who may or may not be interested in helping out. There's no easy mechanism to provide a carrot for that help to appear.

So I think the suggestion of trying to tap into other means of discovering across the nation adverse drug reactions, and particularly working with some of the HMOs that have large clientele and computerized systems for tracking such events, is really an idea whose time has come. I don't think if you're really interested in looking at post-marketing, rare adverse drug events, that AERS alone is going to do it.

DR. TUCKSON: Well, let me just say that I will give you the name of the contact off-line since I've got to be careful. One of my subcompanies is a company called Engenics, and they actually collect and send that information, post-marketing adverse events, based on a database of well over, I think, 70 million people. Anytime any new drug comes out, they monitor that pretty much and then feed it back to FDA and others. It's called I3, and so without doing any further conversation about it, I'll do it off-line and you can go to them independently and find out about that.

So I think Francis is right on the money there.

Julio, I think you hit it and there are things that we can do.

DR. WINN-DEEN: So, again, we should have some recommendation to deal with both the HHS database through MedWatch, as well as through any private databases that we have for surveillance, to try and identify things early and get people enrolled in a study that might lead to understanding how that event came to pass. I understand there are huge issues when you only have 10 adverse events and 500,000 SNPs you might want to do on a HapMap-generated whole-genome association. There are some

real issues in never finding anything, but we should at least try and put mechanisms in place.

Gurvanee?

DR. RANDHAWA: I was curious. I agree this is an important area to investigate. As part of the benefits and harms calculation, if we can figure out using pharmacogenetic testing how we can reduce harms, that's wonderful.

The flip side of it is we can also use pharmacogenetics to identify non-responders. Is the committee thinking of making a separate recommendation for that, and if you're thinking of creating a national registry of outcomes -- adverse events are essentially outcomes -- why can't we have efficacy and effectiveness outcomes also to see where the drugs actually didn't work. That might also save a huge amount of resources that may have been spent not very well.

DR. TUCKSON: Do you see that sort as collected at an aggregate level for study purposes for precision on the advice and guidance of how to use the drug?

DR. RANDHAWA: Absolutely. I think that is what I was alluding to also before lunch in prospective studies. If you can get a sense of is there a (inaudible) there before we do that, then we can go ahead with work conditions, what genes, what drugs.

DR. WINN-DEEN: I think one of the conundrums that the community has faced for some of those things is that some of the genotypes are not 100 percent predictive. So what do you do with someone who's predicted to not be a responder, but you know that 30 percent, let's say, of the "non-responders" actually do respond. Do you withhold the drug from them? There are some ethical issues that you get into when it's not a real yes/no kind of response from the genetic analysis. So we also have to somehow deal with those issues as well because I don't want to get in a situation where you're denying someone a drug that they might benefit from.

DR. RANDHAWA: I agree, but usually we have more options than not. So you can always think of changing the class of the drug or a different drug. It's seldom the case that there will be just one drug that has to be given or not to be given. But I agree with your point.

DR. WINN-DEEN: So you're saying that really, instead of not giving them a drug, you'd give them a drug that they're more likely to respond to than the one that you were considering. Choosing among a set of three, which is the best one for this patient, is a different story than saying the only option is drug 1 and you're not going to get it. So we just have to keep in mind all of those ethical scenarios as well.

I think that we can move on. The next section was on incentives or barriers to companies to co-develop drugs and pharmacogenetic tests.

Certainly one of the issues is coordination of the timing, and I don't know that even if Steve comes up with an improved version of the companion diagnostics white paper, you're still going to have that issue of how do you know soon enough to get a test validated and ready to go in the clinical trial.

But we can potentially deal with this issue of, I'll call it, the disconnect between the orphan drug

designation and the orphan device designation where you have an orphan drug whose threshold is quite a bit higher than the 4,000 cases that puts you in the orphan device category. So I don't know if FDA, within your knowledge base, has had any internal discussion about how to rationalize that disconnect.

DR. GUTMAN: If there have been, I'm not aware of them.

DR. WINN-DEEN: So that's an area where I think we could potentially ask for FDA to look at whether, if something becomes an orphan drug because it works only in a small set of patients, that the test that goes with that drug also gets the same orphan status and be allowed to get through, rather than having to face the much more difficult threshold of 4,000 tests a year for 4,000 individuals a year.

I think the concept of using orphan drugs, orphan devices to deal with subpopulations of folks who are, let's say, a small minority population but that could have great benefit from something is one that we don't want to ignore, if there are things out there. Again, to the comment that Gervaneet made earlier, that if the power of your overall population efficacy is driven by just a small number of people who really respond well that are mixed in with the total, you really want to understand that difference. Is it really 60 percent of people respond or is it that 10 percent of people really respond? And if so, can you make the financial incentives for making a drug and a test for that drug attractive enough that the private sector will go for it?

Changes to the Orphan Drug Act is getting into Congress, I'm afraid, and not just HHS. That's true. Right?

MS. CARR: Well, you could suggest that the Secretary propose changes.

DR. WINN-DEEN: My biggest thing here is that if we're going to put pharmacogenetics or some kind of a subpart in that gives orphan status to one part of the health care, it ought to give orphan status on both sides. I'm not quite sure how to say that better. I think that was really what we're trying to do, and we also want to make sure that the small subsets of people who could really benefit from something aren't denied it because it's just financially unattractive for companies to commercialize.

Any discussion on that recommendation?

(No response.)

DR. WINN-DEEN: Moving right along, the next section was on infrastructure, and we've talked a little bit about infrastructure already in terms of needs for what's out there already, what kind of surveillance would be useful. The question, I guess, before us is what additional infrastructure do we think is needed, if any.

So we had under this infrastructure a recommendation to incorporate basically genetic analysis in both the drug approval and the post-marketing process and, as such, encourage more wide utilization of pharmacogenetics. So I think this goes back a little bit to what we said in the earlier part about funding translational studies. I don't know. Maybe those two recommendations can be merged together there.

Any other comments on how we should deal with that issue and recommendation?

(No response.)

DR. WINN-DEEN: Good. We might get out of here early.

DR. TUCKSON: If there's no comment on it, is it because we don't think it's a priority or you like it?

DR. EVANS: I would echo what I think was just said, that perhaps this should be rolled into that first recommendation. My personal view is that this is perhaps the most important thing.

DR. WINN-DEEN: All right. We'll note that.

Direct-to-consumer. There obviously is a little bit of work going on in this area already. It's not directed just at pharmacogenetics, but more broadly the FDA and FTC are working together to look at false claims for any type of genetic testing. I don't know if there are additional things that we want to do or if we want to, as is outlined on page 6, address the fact that things are already happening. We've already written letters to the Secretary. As a result of that, we're pleased to see that there is this joint task force in place between FDA and FTC.

I guess the next thing that that task force could be doing -- and we can discuss this -- is whether we want to try and encourage them to provide some kind of advice to consumers, things to watch out for about genetic tests in general and maybe pharmacogenetics. I'm a little less concerned about pharmacogenetics because it's not that likely that they're going to be able to get the drug that their test told them to take without seeing a physician.

DR. LEONARD: No, but they could change their own dosing.

DR. WINN-DEEN: Yes, that's scary.

DR. LEONARD: Yes, it is scary.

DR. WINN-DEEN: So, Steve, where do you guys stand on actually getting to some consumer alert kind of thing? Would it be helpful for us to say that that would be useful, or are you doing it anyway?

DR. GUTMAN: We're working on a consumer alert, and it is not immediate but it's in the very near-term future. So once it's published, if you decide that more is needed, then perhaps at the next meeting, you could say, well, that's a nice start, but here's what you should do. But you probably should wait and let us get it out.

Once we get it out, we will try to -- I imagine FTC has mechanisms for distributing those things. We certainly will link it every place we think appropriate and try to get in Reader's Digest or something. It pays to advertise. I would at least let this run its course. I think it's a first step. Whether it's enough or not is a different question.

DR. WINN-DEEN: So then I think we probably should just change our paragraph basically that indicates that that is imminent and that we're in support of that concept, and if we have any further

recommendations, they'll come. Do you think that will be out before the June meeting?

DR. GUTMAN: yes.

DR. TELFAIR: Can I say something?

DR. WINN-DEEN: Sure, absolutely. Joseph.

DR. TELFAIR: Just on the other side of the consumer alert part, we could as a committee look at the composition of the alert itself. But I'm just wondering. Do we also have an obligation to make sure that there's an understanding on the other side related to that and that's something maybe on our list of things to do as follow-up to get -- I'm not quite sure how to word this. So I'll just say it and then maybe someone can help me word it.

I'm just concerned that the consumer side of the consumer alert be involved in the process of --

DR. WINN-DEEN: Right. So we have some stuff as we get to education, where we talk about consumer education. Is that what you're talking about, making sure that they understand, if they saw the words "pharmacogenetic test," even what it means?

DR. TELFAIR: Yes. If we already are covering that, then never mind.

DR. WINN-DEEN: Yes, I think we have some things coming up in the education part of that to address those concerns.

Agnes?

MS. MASNY: Just another point that we had already discussed on the other one about the regulatory issues of when something should be included in a drug label, that maybe just a consideration of when a consumer alert should go along with something that's going to be in the drug labeling.

DR. WINN-DEEN: So if a drug label changes, should a consumer alert be put out by FDA or whoever to people taking the drug already.

Do you guys have any kind of policy on that for when it changes?

DR. GUTMAN: We have an extensive system of alerting. I think it is more directed at the physician than at the patient unless it's an over-the-counter product, in which case we would probably be quite interested in reaching the patient.

Again, I don't have enough experience to know whether that would be perceived as an incredulous burden or a wonderful opportunity. I just don't know.

DR. WINN-DEEN: Other comments? Go ahead.

DR. TELFAIR: I'll say this and maybe repeat it when we get to that. The recommendation is to make the information more consumer-friendly, but I'm just wondering also if there should be just a

specific comment related to coordination of that information because if consumer alerts come out intermittently, then there needs to be some way that whatever efforts are being put into making it more consumer-friendly or more user-friendly, that it's coordinated with the alerts as they occur independent of whoever it comes from. There needs to be some level of coordination. So I would expand the recommendation a little bit to make that because I think that if we did that, there's a degree of assurance that goes with that.

DR. WINN-DEEN: Do we need to make sure that our consumer alert is the first thing that comes up when you do the Google search so that the consumers are getting that information before they get the other marketing information on direct-to-consumer?

DR. TELFAIR: It makes sense that you would have that, to have some kind of clarity on that because the marketing could be very well done, but understanding leads to more informed use.

DR. WINN-DEEN: Sure.

Debra?

DR. LEONARD: It will be interesting to see what your alert says. But you require drug labels. When we develop an in-house developed laboratory test, you require labeling on there to say what it is. Can there be labels required on these websites that meet your alerts and standards?

My concern is if you alert a consumer that they should take this information to their physician who's giving them the drug so that that physician can make appropriate dosing decisions, then those physicians aren't going to know what to do with it either. You can tell the consumer not to change their own drug dose or not to stop taking a drug based on pharmacogenetic information, but they're going to want to do something with it. And probably the only recommendation you can make is for them to go to their physician who's giving them the drug because they know the other drugs that they're on and how those may interact. But most physicians aren't going to know what to do with pharmacogenetic test information.

DR. GUTMAN: Yes. No, I think that point is well taken. I think that we had as a view making this user-friendly and actually doing, I think, what you're suggesting, alerting people not to start self-adjusting meds and to talk to their doctor. I don't think we actually had as a fundamental precept here that we would actually give their doctors brains.

(Laughter.)

DR. LEONARD: You don't have to give them brains, but you have to give them dosing information, which is what's lacking and it goes back to this ultimate --

DR. GUTMAN: Well, but you have to realize that some of this information is being generated and there is no dosing information because some of this stuff actually isn't -- well, I want to be kind, but some of this stuff is just too bizarre for words.

The problem wasn't that we didn't want to go after them. The problem was they couched their advertisement in very clever ways and made it very hard to posit a risk. Whoever they hired were very

good legal or advertising staff, and they made it very difficult for Matt and very difficult for FDA to be able to find the kind of smoking gun that would allow us to take stronger action. So this consumer advisory is a second choice. It's not a first choice.

DR. EVANS: Just parenthetically, I think the bigger risk is one that is out of the purview of the FDA and that is that what is really gaining momentum in the lay world I think is the whole idea of individualized medicine, and there's a whole cottage industry of snake oil salesmen now selling things like nutraceuticals and that type of thing based on your DNA analysis. You can send in a cheek swab.

DR. LICINIO: Face creams also.

DR. EVANS: Yes, right. You name it. Spas do this, et cetera.

So that's a bigger issue that goes beyond pharmacogenomics, but pharmacogenomics is one subset and is much more regulatable and much more tractable than that. But it's something that in the future the committee might want to think about.

DR. WINN-DEEN: Well, I think we actually have looked at that, and that's part of what FDA and FTC are surveilling. So, again, to the comment that was made earlier today, if you see any gross, just total lying in advertising kind of things, please bring them to the attention of our liaisons to FTC, to FDA, to Steven and Matt, and they will incorporate them.

DR. GUTMAN: Again, I'll recap the history that when we started looking, what we think may have happened -- maybe this is delusional and we think we have more might than we do. But we started going on websites using computers that were identifiable as FDA computers, and the websites started to change and disappear. Now, that doesn't mean they didn't crop up elsewhere. But, in fact, we spent a great deal of time preparing what we thought was a great case for Matt, and when we went to do the final check, it was gone.

DR. WINN-DEEN: Self-policing, right?

I'm going to try and move us along here so that we can get through all of this stuff.

The next section was on coordination of efforts. We certainly have had a lot of discussion about the continued need for coordination of efforts among agencies and even potentially with groups outside of the U.S.

Apparently there has been some discussion about the appointment of a genetics czar or coordinator. I personally don't recall that discussion, but it was there somewhere, I suppose, since staff has this in here. Do we feel that the field of pharmacogenomics requires some particular assignment of a person within HHS to act as the coordinator, or does HHS generally find its way to creating the right kinds of subcommittees and things? I'm going to ask the people who are within HHS whether they feel like they sufficiently coordinate among themselves or if they would find it helpful to have someone who was a designated go-to person to just make sure things are happening.

Oh, sorry, Francis, did I take your --

DR. LEONARD: He doesn't officially have the title of czar.

DR. WINN-DEEN: You know, being a czar is a double-edged sword because the last czar, as you know --

(Laughter.)

DR. COLLINS: Be careful what you ask for. Look around the government recently and tell me where is an example where the appointment of a czar has actually led to a good outcome.

So are we not better off to try to continue this effort to coordinate between agencies by people who are already committed to this, rather than somehow making that somebody else's problem, which will then provide, if anything, a disincentive to the agencies to try to work together because it's somebody else's responsibility to see that happens? So I have to say I wouldn't be very enthusiastic about this idea.

MR. DANNENFELSER: I second that. I think there's a tendency to layer on too many new layers of bureaucracy in some of these cases, and I think you want to limit the amount of times that you call for that. So I would agree.

DR. BRADLEY: I would agree. I think from my perspective, which is very short within the government, but still, I think there has been increased cooperation. We certainly have been working with a number of different agencies on EGAPP and other things that were initiatives within our office. So I think there's quite a bit going on actually between the agencies.

DR. WINN-DEEN: Well, I'll take that as one we can strike from our list.

On a personal perspective, the things that we've asked from this committee to see coordination on I think have all resulted in coordination of activities. And I think if we can continue to highlight bringing together information so people know what's going on in other agencies, my perception is that a lot of times it's not a desire not to cooperate, it's just a lack of knowledge that there is something going on in parallel. So I'd like to encourage this committee to continue its mandate to encourage that kind of public exchange of information so that all that stuff is out on the table.

Part 2 of this recommendation or potential recommendation --

MS. MASNY: Emily, the only question that I have on this about the coordination and that was the international aspect. Is there any need to include that in what's happening in HHS?

DR. WINN-DEEN: Does anybody from HHS want to talk about that? It seems like we're getting that when we need it, but it's more on an as-desired basis.

DR. COLLINS: I think actually the lines of communication are pretty good in the field of genetics, maybe in part because the Genome Project itself was international with major involvement by six countries. The HapMap was itself international. Six countries were involved in that as well. At a scientist-to-scientist level, a lot of connections were built and strengthened that are going to be quite durable. And I think at the agency level, the U.S. agencies learned to work quite productively with their counterparts in the U.K. and in Japan and China and Canada, Germany, and France. So we could always

look to see how this could be better, but I don't think at the moment that this is a major problem.

MR. DANNENFELSER: To the extent you might have to involve the Office of Global Health Affairs at times in this, the director of that office already has a Global Health Policy Core Group that involves most of these agencies within HHS. So I think you already have a mechanism there, that you could get it on that agenda, if you had to. So I don't think you need to bring something new in. I think there's something there. You just have to tap into it when it's needed.

DR. WINN-DEEN: All right. On to clinical practice, factors influencing uptake. So, great, we have the data. Now can we get it to become part of clinical practice?

There are a lot of educational efforts underway I think. We've made our comments as a team on that. We've sent a memo up to the Secretary about the need for continuing genetics education in general. And I certainly would view that pharmacogenetics is not an exceptional subset. It's part of that learning how to use genetics information to better manage patients.

I guess the question we have is whether we think that there's an easier path or an easier message maybe to carry forward, less scary message associated with teaching people about pharmacogenetics and maybe more immediate applications than the perceived "specialty" of dealing with people with genetic disease, which is a much smaller percentage of the population.

Certainly when we get to the genetic component of common complex disease, we'll be dealing with, pretty much, anyone and everyone. But the whole field of genetics has sort of evolved from this real specialty where you just deal with the monogenic kind of diseases that are pretty rare but highly penetrant.

This is sort of the middle case of trying to get genetics out into society more broadly. Is this a good way to start doing more broad education so that when we do have the common complex disease stuff, that things are already in place in terms of people have heard the words and maybe they've even had a test at some point to help personalize their medicine?

So the question is, do we need to anything more than what we've already done, which is to encourage that genetics education continue to be funded pretty much all the way through K through post-grad and even continuing medical education for health care professionals who are done with their formal schooling? Or is what is going on already, as part of the overall education sufficient?

Any comments? Debra?

DR. LEONARD: Well, I find this a little problematic because I'm not quite sure what we'll be telling them, when we are missing this final step of you do the test and then this is how you change the dosing, if it's a dosing pharmacogenetics that you're talking about. If it's a right drug in the right patient like Herceptin and HER-2/neu, that's relatively easy to educate about.

But I'm just concerned, given that a number of us have said that the highest priority should be these prospective outcomes trials, funding of those, so that we know what to do with this data clinically, that if we start advertising, and yes, you can have the test done, and no, we don't know what to do with it, it's not going to be a very good education advertisement.

DR. WINN-DEEN: Yes. So I'm not sure we should be advocating advertising anything until we have all our ducks in a row. I think the question is just as these ducks come into focus, one after another, each one of them offers an educational opportunity to help people learn. So we have 2D6 and Straterra. We have UGT1A1 and irinotecan. We have TPMT. We have the warfarin story. We're starting to get maybe one or two stories a year coming into play where things are moving beyond the experimental and into more of the "routine." So should we be encouraging, as these things move into that realm, that each one of those is an educational opportunity?

MS. CHEN: I think for the public, it's a little bit too premature as an educational opportunity, but definitely for the physician, especially if they're going to be prescribing these kind of services, or not prescribing, they are going to send the sample to do these kind of services, I think they should know what they're about and they should be trained how to make this kind of decision or talk to somebody to make a better decision. For just the general public, it's just too early in the game for doing that.

DR. EVANS: Yes, and I would echo that. I think about HER-2/neu and Herceptin. Frankly, educating the general public about it is, in many ways, kind of silly because it's applicable to so few people. On the other hand, educating physicians and providers about it is incredibly important.

My feeling is that once the ducks are in a row and once efficacy has been established and we have good studies, which, of course, is an earlier recommendation, that number 8 is a great recommendation because I think it's true. I think that there are fewer stigma and potential ELSI kinds of problems with pharmacogenomic data, and therefore, it's a very good issue that we can sink our teeth into. We can educate and we can help the medical establishment roll out something that is not particularly threatening and is useful. It's low-hanging fruit.

DR. WINN-DEEN: So if I understand basically your comments, the education would be first to the physicians and then allow the physicians to educate their specific patients that would benefit from it and do it in a more targeted way in that way, rather than trying to do any kind of generalize public education at this point.

DR. EVANS: Yes. I don't think the public will feel cheated if they aren't educated about drugs that most of them will never use.

DR. WINN-DEEN: But are you watching the Lipitor commercials?

DR. EVANS: Yes. According to many people, it should be in our water. Everybody should get it.

DR. WINN-DEEN: I think the drug companies are out doing a little bit of education for us as well.

There are comments down at this end. Gurvaneet.

DR. RANDHAWA: I think it's an excellent recommendation. My only question is who does the education and at what stage. Part of the "who" is we all heard about the evidence should be there, the ducks should be in a row before we do the education. To me, that means there should be some sort of a professional society or organization that has a guideline on that area, and then that guideline can be

disseminated. So if it's an oncology drug, there's the American Society of Clinical Oncologists or some specialty society, or even if it's a general practice, there's the American Academy of Family Physicians, American College of Physicians.

I think we need to get a process in which, once the evidence is there, there's a short time line in making evidence-based clinical guidelines. EGAPP is doing a very good job in making some progress there, but that really is what we need, buy-in from professional organizations at the beginning. And then who does the crafting of the message can be done in concert with them, not independent of them.

MS. MASNY: I was going to say something very, very similar to that and then actually ask Linda regarding the EGAPP project, whether there will be some type of education process with the findings of what you have from your pharmacogenetic study.

DR. BRADLEY: Yes, it will come out in several different forms. Obviously, there will be an evidence report from the EPC, the Evidence-based Practice Center, and a publication that will come out that, and then there will be recommendations that come from the EGAPP working group.

In addition to that, we've spent a long time talking about how those sort of technical and maybe not very applicable to the general population messages get translated and sent out. We're actually working with some folks to talk about how to do that.

So, yes, we do plan to do that. I couldn't tell you exactly what form that's going to take at this point, but it's definitely needed or the messages will be lost on a lot of people.

DR. WINN-DEEN: So our next recommendation really is very similar to this, about recommending mechanisms to make the PGX information more user-friendly and likely to be accessed and used. So I think we probably could roll those two things together and talk about this mechanism of determining utility, having it go to the appropriate clinical groups for recommendations, which then educate their physicians, who then educate their patients, and sort of doing this trickle-down educational approach, at least for the near term until it becomes so widespread that everybody should just know about it because eventually something is going to come up that they need.

DR. TELFAIR: Well, earlier, remember the thing of the reverse of the consumer alert?

DR. WINN-DEEN: Right.

DR. TELFAIR: Wasn't this this recommendation, which is number 9, something that was referred to as a way to address that as well? So if we combine the two and you combine it as you have laid it out, what does that change?

DR. WINN-DEEN: Well, I guess the question that we had is to what extent can you expend energy educating people who aren't going to ever find this relevant in their lives. So I think the point that several of the people have made with regard to how to deal with public issues, is at the point where they are going to be engaged, they also need to be educated. I agree with that. The question is just, I think, a matter of mustering resources. Can we afford to create educational campaigns, beyond just the basic incorporation that genetics is a part of your life, into all of the education, K through whatever. Can we do targeted campaigns for pharmacogenetics? I think what I've heard is that we think it's not time to do a

broad consumer campaign on pharmacogenetics at this time or to recommend that.

We have a few more recommendations to get through, so I'd like to try and move along.

In terms of the physician, can we get recommendation 10 please? Again, this comes back to how do we get the information the practicing physician needs to make it relevant to their clinical practice. That includes having an understanding of how to identify what patients might benefit and then knowing what test to order and then knowing what to do with the test result when they get it.

Steve, you said that most of the drug labeling changes, when labeling changes come, that there's a system for educating physicians. This might be a good time to just clarify what you know about that.

DR. GUTMAN: Well, it would depend on the nature, but it could be as much as an actual mailing if it's a significant enough alert or concern. The physicians here must all get these. There is, of course, a tendency to throw them away and not read them.

(Laughter.)

DR. GUTMAN: But I'm sure no one at this table does that.

I would imagine that more subtle changes, ones that aren't substantive, probably are put in the labeling without the same level of alert. So I think it's a matter of risk management and degree, but certainly significant changes the agency actually attempts to leverage through the drug firms. It's the drug firms' responsibility to provide that information. If the drug firm seems unwilling, then the agency is happy to help.

DR. WINN-DEEN: Right. So I can definitely see in the detailing of a new drug, if there's a test required, that the pharma rep is going to teach the physician all about the whole thing, hopefully, that they need to order the test, and then they need to order the drug because it's the greatest thing since sliced bread. So I can see how that happens.

Do you understand how it happens when there's been a label change so new information about an existing drug --

DR. GUTMAN: Well, I would argue that, again, it's a risk-based stratum. It would be the same thing. If the label change was a weak one, then I think there would be less incentive to make sure that everybody got the word. If it was a really significant labeling change, I actually the agency would create some kind of communication plan collaboratively with the drug company to try and get the users to get the word out.

FDA has actually a lot of risk communication strategies. I don't know about Drugs, but I know in Devices we have lists of ob-gyns, list of pediatricians. We'll actually develop targeted mailings based on what subpopulation of the health care professional community we're trying to reach.

I'm not sure that just because a drug is not new, that there aren't people who are detailing or who are selling it. So I think that there probably are very complex considerations taken as to how you would do that.

But certainly I know and love the people in Drugs, and they're just as passionate about their products as I am. So I'm certain that if they made changes that they thought were relevant to the safety and efficacy profile of the drug, they would be very concerned with trying to get that message out.

DR. EVANS: I would echo what you said about the inadequacy of our current ability to get through to physicians about changes. I don't think that's the fault of the FDA. I think it's probably the fault of physicians. But it's a huge problem.

I would add, for whatever it's worth on this, to explore the potential for existing and novel partnerships. I think this whole realm that we're dealing with in genetics calls for novel ways of getting information to physicians because physicians have a singular fright of things genetic, and they really feel like they don't understand it well. It's not going to be enough to mail them things because they throw them away.

MS. CHEN: Could I make a recommendation? Every year, or I don't know how often, doesn't a physician need to take classes? And this could be part of the classes.

DR. EVANS: They can take whatever they want.

MS. CHEN: Could it be put as a requirement that you have to take certain ones?

DR. LEONARD: The only way would be to have pharmacogenetic testing included in the recertification process because everybody has time-limited licenses now. So that would be the only way.

MS. CHEN: That would be great.

DR. LICINIO: I know this is an investment for the future, but another suggestion might be to talk to the American Boards of Medical Specialties and request that at least some questions on pharmacogenomics be included in the boards and that be part of the topic that people have to know to pass their boards.

DR. RANDHAWA: Yes. I would suggest another and perhaps a little bit more efficient strategy would be, in terms of where we're moving with health information technology, e-prescribing, pop-up alerts, whether it's through your PalmPilots or on the computer screen, that as and when new pharmacogenomic testing becomes available with adequate evidence, that this become a part of the algorithm or protocol for giving the drug. When the physician is to prescribe warfarin, there's a pop-up screen that says have you done a test for such and such genes. So it should be a part of our new ways of disseminating information and making it part of the clinical protocol.

DR. WINN-DEEN: I'm afraid that a lot of the physicians who might be the most recalcitrant are not using any of those electronic-driven things.

DR. EVANS: I would agree with you about the pop-ups and all, but working perhaps through the formularies. There are many agents that formularies at hospitals have some control over. It might be reasonable to envision ways that when a physician prescribes agent X, Y, or Z, that there's a reminder, a call, an e-mail, whatever, about the need to do testing.

DR. LEONARD: I hate to lump, but couldn't 10 be included? It's very similar to 8 and 9. It's basically educating. So can they all be combined into one recommendation?

DR. WINN-DEEN: Well, I think what we'll try and do is we'll try and listen to all this feedback and then reconstitute these recommendations in a way that makes sense, whether it's one, two, or three. Each of these little statements was really designed to engender some discussion and feedback so that we could get to what the real things we want to say are on each of these subjects.

MS. BERRY: Related to this last point, though, I know, for example, the American Heart Association has developed, in conjunction with agencies and with the cardiologists, a variety of groups, these clinical decision support tools for the treatment of cardiovascular disease and stroke, heart attacks, and whatnot. So these start out as hospital-based programs where they can develop a very specified, specific treatment protocol for a patient and there are prompts on the computer that assist a doctor in coming up with those things. Then there are patient education materials that are generated upon discharge and whatnot.

I'm wondering if some of these groups, like the Heart Association and others, and those that are engaged in clinical decision support tool development, could weave in pharmacogenomics in whatever it is they develop. I think also these things might have been developed in consultation with JCAHO and some of the other accrediting agencies. So maybe some of those agencies could be involved in some way that would facilitate or encourage the integration in clinical practice.

So that's just one area, and since heart disease affects so many people, diseases like that might be a good place to start. I don't know how it exactly weaves into the recommendation, but it's a little twist, anyway.

DR. WINN-DEEN: I'm going to try and skip ahead a little bit here. The next couple sections I think we've actually already covered in fairly good detail. The next proposed approach 11 dealt with ways of representing populations in clinical trials and assuring diversity in the clinical trials. I think we've already gotten quite a bit of feedback on that subject. So I'd like to skip over that one.

Proposed approach 12 again had to do with how to remain compliant with current regulations. I think we can work on a recommendation that basically says people should be compliant with current FDA and NIH guidance, depending on what kind of study they're running.

We have about 12 minutes by my watch. So we've got a few more recommendations here.

One thing I'd like to discuss a little bit is the section on liability and its influence on standards of practice, and particularly since Cindy is here today, to get a little bit of a view on how much we think the liability factor might be a driving force in leading to adoption of these kind of tests. At what point does something "become standard of practice," and do physicians leave themselves open to malpractice suits if they don't implement something? I don't know if there's anyone else that has experience or expertise to lend to that discussion, but it certainly seems to me that it's an aspect of what drives physicians to adopt new things that we can't really overlook.

So is there anyone that has any light to shed on that subject? Agnes?

MS. MASNY: Just a comment about liability driving the practices. For irinotecan, in one of our noon conferences, they brought up the discussion about this testing for the UG2A1A. Most of the physicians there felt that because it was already on the label, then they were obliged to provide the test because if they didn't provide the test and if someone had a toxic reaction, then they would be liable for not providing it, since it was already on the label. So I think it was just as a comment that this is a very clear concern that once something appears on a label, then physicians are liable then to provide that test.

MS. BERRY: The crafty trial lawyers will come up with new and innovative ways and use this. If someone does a test and they determine that an individual patient is not a candidate for a particular therapy because of some gene or whatever and the doctor explains that and they don't give them the therapy and there's a bad outcome, some lawyer could say, well, you should have given the therapy anyway. And then if they do give it to them, and there's an adverse event, it's sort of a no-win situation.

Then somewhat related to this, these controversial cases that are coming up about obstetric screening and testing and whether the child has some kind of anomaly or problem and if they misinterpret the test or they don't give the test and they did a wrongful birth. There are things that are popping up in the legal system that are going to be difficult to manage.

So I would say that we should do our best to recognize that that's out there, but we shouldn't let it thwart what we think is the best practice of medicine that would help deliver the best, most appropriate patient-centered care. But we should always keep in mind that there are these people out there trying to take advantage of science and, unfortunately, create some weird incentives in the delivery of care. We're always going to have defensive medicine because of it. So, unfortunately, I don't know that we could shield the medical profession from that. We just have to be cognizant of it.

DR. WINN-DEEN: So do you think it's important for us to, for that reason, perhaps err on the side of conservatism in terms of when things are put into an FDA -- I mean, from a patient point of view, you might say, put it in as soon as you think there might be a reason to test, and from a legal liability, you might say, put it in after you're really, really sure. Somewhere in there is the right time to put it in depending on what you're thinking about, what's driving you.

I hate the idea of health care being driven by lawyers, but I recognize that there's a certain reality to that.

MS. BERRY: Well, then linked to all of it is the coverage issue as well. The threshold for a health plan or for a federal health program to cover something may be different from what FDA might initially recognize or acknowledge in a label. So that would affect whether a patient receives certain tests and a certain therapy.

And then do we exacerbate existing disparities when maybe a health plan won't cover it or the Medicaid program won't cover whatever it is? A patient of means could still pay for it out of pocket and obtain it, but someone who is on a health program, government program, and they don't have the means, they don't receive that. Then what are the problems there?

DR. WINN-DEEN: Right. Well, access to good health care is, I think, one of our overarching issues that we have to deal with here. I think part of the incentive for developing pharmacoeconomic arguments is to look at the overall episode of care and understand that, hopefully, if a test costs more up

front, it also leads to a lower overall cost because you get to the drug treatment more efficaciously, earlier, or whatever. But those kind of studies, which are needed really to justify making sure everything is covered all the way through, are sort of long in coming.

MS. BERRY: But is the label the place for this, or is it more in the technology assessment coverage arena?

DR. WINN-DEEN: So I guess maybe we could highlight that there is and remains a disconnect between FDA approval of a test and FDA changing of a label and coverage and reimbursement. Those two activities happen as separate evaluations, and until they're linked, there will be these disconnects on access.

I think we certainly brought that up during the coverage and reimbursement discussions, and it's clearly enunciated in that report, but maybe we also want to make sure it's in this report as well, as one of those overcoming-the-barriers things. I think we have something on that in the overarching issues.

MR. DANNENFELSER: I'm not remembering the term, but I remember when we were going over this coverage and reimbursement. Aren't there some threshold terms with CMS in terms of this? And I'm just wondering how that relates to what Cindy is saying, that perhaps the fact that it is in the label, that there is a medical indication or whatever, a medical basis for doing such a test might then give CMS reason to cover that test for people or whoever might need it.

DR. WINN-DEEN: Well, I think that's all part of the evaluation. I'll let James talk about what the threshold is.

DR. ROLLINS: In terms of threshold? In terms of what? Sensitivity or?

MR. DANNENFELSER: No, no. Whether CMS would provide reimbursement.

DR. ROLLINS: Well, currently CMS only pays for diagnostic testing, and a patient has to have signs and symptoms of a particular condition. If a patient has a family history of a particular disorder and if the patient does not have signs or symptoms of the disease, then they won't pay for it because they consider it's screening or preventative. Even though the FDA may say that this test has been shown to be effective for diagnosing X, Y, and Z, as I say, if the patient doesn't have signs or symptoms of it, Medicare will not cover it.

DR. LEONARD: Where does pharmacogenetic proper dosing testing fall into that arena? If a physician is determined that a patient needs a drug and there's a label on there saying that these certain genetic variants predict proper dosing, where does that fall in CMS's realm to pay or not pay?

DR. ROLLINS: As far as I know, Medicare does not address the threshold for proper dosing, but it does acknowledge that if a patient has, like for example, TPMT, from what I've been told, yes, because a patient does have signs and symptoms of the disease, this test can be used to monitor the patient's condition, to determine whether or not the patient is getting a toxic dose or an insufficient dose.

DR. RANDHAWA: Being neither in CMS nor FDA, I'm probably the best place or worst place to make this comment. If you look at the criteria, FDA looks at safe and effective. If you look at CMS,

it's reasonable and necessary. So there is no way you can ever get 100 percent concordance between these two. That is how Congress mandated it and that's how the agencies are carrying out their missions. So I think there's a fundamental issue there about the evaluations that are different in the two agencies.

DR. WINN-DEEN: Right. So I guess what we need is these translational studies that demonstrate both improvement in safety and/or efficacy and that it would be reasonable and necessary for a patient to have that test in conjunction with taking a specific drug. So maybe when we do these translational studies, we should really consider both of those aspects in the study designs and try and deal with both those issues.

DR. EVANS: I guess you can postulate that anytime somebody is going to be getting a drug, they're showing signs and symptoms of a disease, or they wouldn't be getting it. So does that mean that these tests would be paid for then, I mean, in the same way that TPMT testing is paid for?

DR. ROLLINS: I would hope that the patient would get the medication when it's most appropriate, when he had the disease, but I can't guarantee that all the time. But as I said, if a patient is having signs and symptoms, then it's considered a diagnostic test and it would fall under that.

DR. WINN-DEEN: We're going to have Debra and I believe one more comment to the floor, and then we have to wind up for the day.

DR. LEONARD: One more aspect of liability is if you do a pharmacogenetic test that is for a particular dosing of a drug, it has implications for dosing of a lot of other drugs. So what is the liability there if you have information about the potential to overdose someone with one drug and you give them another drug that's metabolized the same way and you don't take that into consideration? So at least we're talking about using pharmacogenetic test information almost as an allergy alert, where it's posted everywhere and everyone would know it, and the pharmacy would have a list of drugs that are also affected by the same thing. So there's another way to look at the liability issue as what about the liability of other drugs or drug-drug interactions.

DR. WINN-DEEN: Right. So this comes back to how do we put things in electronic medical records so information isn't lost over time and you can truly do a genetic test on someone once in their lifetime and have that information retained with them.

Are there any other comments?

(No response.)

DR. WINN-DEEN: If not, I want to thank everyone for their very productive feedback, for all of your thoughts and words, and for really helping the task force to move this report on to the next level.

We will resume tomorrow morning at 9:00 a.m. in this room.

(Whereupon, at 5:05 p.m., the meeting was recessed, to reconvene at 9:00 a.m. on Tuesday, March 28, 2006.)

