U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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

- Fourteenth Meeting -

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Ronald Reagan Building
1300 Pennsylvania Ave., NW
Washington, DC

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C O N T E N T S

P R O C E E D I N G S

DR. TUCKSON: We do want to welcome everyone to the 14th meeting of the Secretary's Advisory Committee on Genetics, Health, and Society. The public, as usual, was made aware of this meeting through notices in the Federal Register, as well as announcements on the website and listserv.

I want to welcome members of the public in attendance, as well as the many viewers who are tuning in throughout the webcast. I do remind the Committee that this is widely viewed on the webcast, and so be on your best behavior.

We encourage any members of the public in attendance who wish to address the Committee to sign up at the registration desk. We are also providing an extended period for public comment tomorrow afternoon specifically to solicit input on the Committee's Draft Report on Oversight of Genetic Testing, which was released for public comment two weeks ago.

Secretary Leavitt has made several new appointments to our Committee. Since we last met, five new experts have joined our ranks. I want to introduce and warmly welcome each one of them.

First, my old friend Mara Aspinall. Mara is president of Genzyme Genetics, where she is responsible for the company's Business Unit, which includes nine laboratories across the United States and operations in Japan that provide diagnostic testing and genetic counseling services worldwide.

Mara earned an M.B.A. from Harvard Business School, and she is not entirely new to SACGHS. She has been serving as an ad hoc member of the Taskforce on Gene Patents and Licensing Practices for the past year. We have appreciated that work very much. Thank you so much, Mara.

Let me also welcome our good friend Paul Billings. Paul is currently a consultant at Lab Corp, where he works on special projects with the company's chief executive officer. Previously, he was Lab Corp's vice president and national director of genetics and genomics. He is also an adjunct professor of anthropology at the University of California, Berkeley. Go Golden Bears. He was a member of the Joint National NIH-DOE Taskforce and the NIH Recombinant DNA Advisory Committee.

Paul earned medical and doctorate degrees from Harvard and completed clinical training in internal medicine and medical genetics at the University of Washington. Thanks so much, Paul.

Paul Miller. Where is Paul? Oh, there you are. Paul, welcome back. Paul is now the Henry M. Jackson Professor of Law and director of the Disability Studies Program at the University of Washington. Before joining the university, Paul was commissioner of the EEOC and, in that capacity, served as the EEOC's ex officio on this Committee. He also served as the White House liaison to the disability community and a deputy director of the Office of Consumer Affairs.

Paul obtained a law degree from Harvard, and I also want to recognize your service on our Oversight Taskforce. Paul, you also have two areas of expertise you are bringing to us. Not only are you our legal eagle on this but you are also our consumer representative as well, and we very much appreciate your involvement.

Paul Wise. Paul, thank you very much, sir. The Richard Behrman Professor of

Child Health and Society at Stanford, and a core faculty member at the Center for Health Policy, Center for Primary Care and Outcomes Research. His work is focused on children's health; health outcomes; disparities by race, ethnicity, and socioeconomic status; the interaction of genetics and the environment; and the impact of medical technology on disparities in health outcomes.

I know Paul's work well. He received a medical degree from Cornell and a master's from Harvard School of Public Health. He completed a residency in pediatrics at Children's Hospital Medical Center in Boston. Paul, we really appreciate your being here.

The Secretary also appointed Rochelle Cooper-Dreyfuss to the Committee. Professor Dreyfuss has a longstanding commitment at the National Academies. She is not able to be with us today, but we want you to know that she is the Pauline Newman Professor of Law at New York University School of Law. She serves as a member of two National Academy of Sciences committees, investing intellectual property issues. She is the past chair of the American Association of Law Schools Intellectual Property Committee.

Before earning a law degree from Columbia University School of Law, Professor Dreyfuss earned a master's in chemistry and worked as a research chemist.

Welcome to all of our new members. Let me add that I understand that you are serving today as ad hoc members of the Committee pending the completion of the wonderful appointment process. In that capacity, you are not yet voting members of the Committee. Nonetheless, you are encouraged, and we will be keeping score of whether you comment or not. We want you to comment.

The other thing that you are graded on is whether you have the courage to say, "I'm sorry. I don't understand where you all are in the discussion. Would you mind taking it back and explaining something because I haven't been here for the 13 years that everybody else has." So that is a good thing.

That is a good thing because I hate it when I come to a committee newly and everybody knows everything and I don't know diddly squat and you feel like an idiot. So I urge you to ask as many questions as you want, and you are more than welcome to participate in everything but the vote, and we will be happy there.

Welcome to the new members.

While the appointment of new members is always an occasion to celebrate, it is often accompanied by departures. This meeting is no exception. Tomorrow we will be saying goodbye to three retirees: Cindy Berry, Chira Chen, and Hunt Willard. So we are going to be sad about that, but we will be sad tomorrow. We won't be sad today.

I want to welcome a new ex officio member, the Office of Public Health and Science. Now, Dr. Inyang Isong -- and she will tell me whether I got that right. Where are you? I got it right? I have never gotten it right.

[Laughter.]

DR. TUCKSON: This is the first time in history.

She is a medical officer and a clinical consultant with the Office of Population Affairs on issues relevant to family planning and adolescent family life. The prior ex officio, Dr. Anand Parekh, is acting director, deputy assistant secretary for health, and has assumed the assistant secretary's responsibilities. We appreciated Dr. Parekh's contributions to SACGHS and look forward to working with Dr. Isong.

I'm really happy that Barry Straube is with us today. Barry is a good, valued colleague of mine. He's the chief medical officer at CMS. Barry is taking a much more direct involvement in our work on behalf of CMS. We know that he can't stay the whole day and can't be with us tomorrow, but Barry is making a very conscious decision by his presence to really, really emphasize how important this work is to CMS. So Barry, I really appreciate your being here today.

I want to recognize an ex officio's contributions in a critical area were honored last month. Dr. Robinsue Frohboese, the principal deputy director for the Office of Civil Rights, with responsibility for overseeing all program operations and policy development, received the Secretary's highest recognition award, the Award for Distinguished Service.

Robinsue, we know that you were honored for your commanding leadership in the Office of Civil Rights and deep understanding in ensuring the rights of persons with disabilities nationwide. I want to congratulate you on behalf of the entire Committee for being recognized in this way, and commend you for your dedication to the citizens of this country. You have dedicated your career to upholding civil rights.

She is of course, after doing that, not here yet. But that is fine because it is in the record. We will remind her that we did this when we see her. But Robinsue is just terrific and great.

Now I would like to update you on a few developments regarding the Secretary's Personalized Healthcare Initiative. In September, the Secretary's Office issued a report on the Personalized Healthcare Opportunities, Pathways, and Resources. You may recall that the Secretary's Office was kind enough to send each of us a copy. The report does an excellent job, we think, of describing current activities that are directed toward the achievement of personalized health care as well as the work that lies ahead to bring it to reality. We commend them for that work.

HHS also released a summary of an expert panel meeting on this topic that took place in March. The meeting was sponsored by the Office of the Assistant Secretary for Planning and Evaluation and involved key stakeholder perspectives, such as payers, representatives from industry and government, and patient advocates.

The discussion identified five main issues that need to be addressed to fully realize the potential of personalized health care. These were, and they will sound familiar to all of you, clinical validity and utility, value and cost effectiveness, the need for data to build evidence and informed clinical decisions, impact on health disparities, and education of providers and patients. A copy of that workshop summary is in your table folder. You can of course download it from the HHS website.

There have also been activities within the Personalized Healthcare Working Group of the American Health Information Community related to the Secretary's Personalized Healthcare Initiative. We are staying abreast of that group's work through the participation of Andrea. Thank you, Andrea, for that. Steve as well, and Marc Williams. So to the three of you, thank you so much for your efforts in this important initiative.

I have been tuning into those by telephone and paying attention to those on conference calls, and the work is very, very important and key to what we are trying to do.

At the beginning of each meeting I have established the tradition, and I'm going to continue it, to take a moment to review our strategic plan and the status of our progress in

fulfilling each of our study priorities. This gives us an overview of what we have accomplished to date and helps us to stay focused. So if we will put that up.

Again, for the new members of the Committee, this was a plan that we as a collective team developed several years ago. It will be, before very long, time to revisit this again.

This is not one of those government committees that just wanders around aimlessly and bumps into walls. We actually have a plan. We actually have a set of priorities. We actually are implementing them, and we keep track of what we do. So hopefully, we will continue in that vein. We may bump into a wall here and there, but we usually know what walls we're bumping into.

The vision statement describing our priority issues and how we reach them was developed in 2004 and continues to reflect and guide our work as a Committee.

Public concern about the misuse of genetic information and genetic discrimination has been our highest priority issue. Over the last four years we have written a number of letters to the Secretary championing the enactment of federal legislation to prohibit discrimination based on genetic information by health insurers and employers. In 2005, we provided the Secretary with a legal analysis of the adequacy of current law regarding genetic discrimination, a compendium of public comments documenting public fears and concerns about genetic discrimination, and a very, very interesting and compelling 10-minute DVD of testimony we received in the fall from the public in 2004.

We have also strongly supported the Genetic Information Nondiscrimination Act of 2007, HR493, and S358, commonly referred to as GINA, which would protect individuals from discrimination based on their genetic information by health insurers and employers. The legislation has dedicated supporters on both sides of the political aisle, and in April of 2007 it passed the House by a vote of 420 to three.

Secretary Leavitt has voiced support for that legislation, and the President has indicated that he will sign the bill if it is presented to him. However, as many of you know, Senator Tom Coburn has placed a hold on the bill in July and thus has prevented debate and a vote in the Senate. GINA's key supporters are working hard to move the bill forward, and the bill's main sponsor in the House, Representative Louise Slaughter of New York, has set up a petition to persuade Senator Coburn to drop his hold. As of today, there has been no change in the status.

In June 2004, we developed a resolution about the importance of genetics education and training of health professionals and how it could be enhanced. Tomorrow Dr. Barbara Burns McGrath will chair a roundtable on genetics education and training for health professionals. Six expert speakers representing various aspects of health care will report on the progress of genetics education and training activities.

These presentations will be followed by a one-hour discussion of critical needs in education and training and the best approaches to meet those needs. Four additional panelists will join the roundtable to extend the range of perspectives from the healthcare community. Then you will be deciding what, if anything, we need to do going forward on this topic and whether we will continue to keep it as a priority and move it forward or to let it go and say that the world is safe and you may all return to your homes. That will be your task.

In 2006, we transmitted a report and recommendation to the Secretary on

coverage and reimbursement of genetic tests and services highlighting how problems in the system are affecting patient access and identifying nine steps that can be taken to overcome the barriers. These recommendations cover a range of topics, including evidence-based coverage decision-making, Medicare coverage of preventive services, the adequacy of current procedural terminology codes for genetic tests and services, billing by non-physician genetic counseling providers, and genetic education of health providers.

In July, CMS sent feedback on the recommendations. A small group of SACGHS members led by Marc Williams has been reviewing those comments. A copy of their review was shared with you in October. We will be taking to our CMS ex officio, Barry, in December our report. I will report back to you at our next meeting about the outcome of that discussion.

Barry, I think you were at the meeting when we presented this to the head of CMS. It was a terrific discussion we had then. I know that you all are taking this matter very seriously.

In 2005 and 2007, we wrote letters to the Secretary direct-to-consumer marketing of genetic tests. This is one of our successes that I'm particularly pleased about. Our efforts in this area led to enhanced collaboration between the FDA, the CDC, the CMS, NIH, and the FTC. In July of '06, a consumer alert was issued by FTC to warn consumers about using at-home genetic tests that have not been evaluated and to be wary of the claims made by the companies marketing these tests.

In July, we also heard from CDC about their work to measure the public's awareness and use of direct-to-consumer genetic testing. As part of the Personalized Healthcare Initiative, an effort is being made within the Secretary's Office to coordinate relevant agency activities and promote information sharing related to DTC testing. Greg Downing from the Office of the Secretary is leading this coordination effort, and we will keep you updated on their progress.

Greg is actually here. Would you wave? Greg has been and continues to be just terrific. We have enjoyed just such good, close access to the Secretary's Office on a day-by-day basis. Greg is the person behind the curtain to make that happen. We are greatly indebted to Greg and his energy and his commitment to the work of this Committee, and I thank him for it.

Concerning large population studies, the Committee's final report, Policy Issues Associated with Undertaking a New Large U.S. Population Cohort Study of Genes, Environment, and Disease, was completed in March of '07 and transmitted to Secretary Leavitt. A downloadable PDF version is available on our website.

In August, the Secretary sent a letter to us acknowledging receipt of the report and the timeliness of our recommendations. You can find this letter in Tab 6 of your briefing books, and it is posted, again, on our website.

I also want to point out that an article about the LPS report was published in the July issue of the journal Social Science and Medicine. Hunt Willard, who guided the development of this report, and I have written a letter to the editor of the journal to clarify the scope and goals of the report. You will find a copy of the article and our letter in your table folder. We have given them a what-for.

For more than two years, we have been developing a report on opportunities and challenges to pharmacogenomics research, development of PGx products and their incorporation into clinical and public health practice. In March, the draft report was released for public

comment. Public comments were carefully considered, and over the summer and fall, a revised draft has been prepared.

Most of our agenda today will focus on a review of the final draft recommendations. Our goal, and this is absolutely key that all of you get this, our goal is to come to closure on the recommendations and approve the report for submission to the Secretary. No fooling around. We are going to close this out and make a report.

In June 2006, we decided to move forward with a study on the impact of gene patents and licensing practices on patient access to genetic technologies. During our July meeting, the Gene Patents and Licensing Practices Taskforce, chaired by Jim Evans, hosted a roundtable of experts to discuss international perspectives on gene patenting and licensing strategies and clinical access to genetic tests.

Since then, the taskforce has been working with Bob Cook-Deegan and his group at Duke on case studies but evaluating the impact of gene patents and licenses on patient access to genetic tests for hemochromatosis, breast and colon cancer, cystic fibrosis, and hereditary hearing loss. We will continue to meet monthly to begin development through this taskforce of a report on this issue, with a final product expected in 2009.

In March of '07, we were charged by the Office of the Secretary with investigating specific issues related to the adequacy of the oversight system for genetic testing. An extraordinary 33-member taskforce, chaired by Andrea -- 33 members -- was formed to develop a report in response to the Secretary's charge.

Now, for those new members, again, the number one issue for us has always been genetic discrimination. That has always been our number one. The number one historical issue out of which this Committee is the successor of a preexisting committee was this issue of the oversight of genetic testing. So this is really in our -- don't get mad -- in our DNA.

So through dedicated effort and exceptional leadership, the draft report was released for public comment on December 5th, with a December 21 deadline for final comments.

Tomorrow, Andrea will review our effort in this area, and then we will have presentations to gather additional academic and public perspectives. We will be briefed on the international analysis of the oversight of genetic testing. We will learn about the conclusions of the summit meeting held on this topic in September by the Genic Alliance, and we will be providing an opportunity for interested stakeholders and members of the public to share their perspectives on the draft report.

I want to make sure that this is absolutely clear. There is a considerable time period for people to comment. The public comment period does not end until December 21. I'm saying it several times. We are having much opportunity for public input. I am trying to be as transparent as I can to every stakeholder in this process. It is an open process, a transparent process. If you are a consumer, if you are general public, if you are industry, if you are a health professional, whatever your particular stakeholder view is, this is an open process with lots of time to get your comments in.

I have reasons for why I'm being as emphatic as I am about it. So I would be very disappointed if there are folk who decide not to be participating in the public process of getting all the best ideas so that Andrea and her 33-person committee can duly deliberate over the best ideas. So I think we have been pretty clear about that.

In March, we decided to add a new priority for SACGHS to explore the issue of

evaluation of outcomes of gene-based applications. This effort combines two proposals presented to the Committee on the economic consequences of genomic innovation and the evaluation of real-world outcomes on gene-based applications. Work on this issue with Steve Teutsch, who will be leading, is on hold pending the completion of our report on the oversight of genetic testing, which includes some of the same questions and issues involved in evaluating outcomes.

So I want to be real clear that this evaluation of outcomes genes-based applications, we have it identified. It is hanging out there. But quite frankly, as you can tell from this very long introduction, we have a whole lot on our plate. We want to get this other stuff done and then we will decide to move on to that.

The cross-cutting issues of access, public awareness, and genetic exceptionalism we have continued to integrate into all of the other committees' work that you have heard.

With that, I hope that you all get a sense, and for the new folk, I hope you don't get intimidated by the amount of work. But we are a very active, very busy Committee. When it is all said and done, when we get evaluated by the Secretary's Office for committees, I want us to be not only the most prolific but the most productive but the most focused and the most intense. I think we are way out in front on all of those scores, so we are going to keep at that.

Are there any questions from anyone before we get down to the heart of the meeting? Let me just take a moment. We have put a lot in front of you. So let's stop for a moment and ask whether there are any questions.

[No response.]

DR. TUCKSON: Good. Well, that will give me a chance to drink my coffee. So that is perfect.

Now for the serious highlight of the meeting, the Ethics Rules Review by Sarah Carr.

[Laughter.]

MS. CARR: Good morning, everyone. Thank you, Reed. You all have been appointed as special government employees to this Committee. Although you are in a special category, you are nonetheless subject to the rules of conduct that apply to regular government employees. These rules are outlined in a document called "Standards of Ethical Conduct for Employees of the Executive Branch." Each of you received one of these when you were appointed to the Committee. As I usually do, I'm going to highlight two of those rules today.

First, conflicts of interest. Before every meeting, you provide us with information about your personal, professional, and financial interests, information 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 will arise that could affect or appear to affect your interests in a specific way.

In addition, we have provided each of you with a list of your financial interests and covered relationships that would pose a conflict for you if they became a focal point of the Committee's deliberations. If this happens, we ask you to recuse yourself from the discussion and leave the room.

Government employees are also prohibited from lobbying and thus we may not lobby, not as individuals or as a Committee. If you lobby in your professional capacity or as a private citizen, it is important for you to keep that activity separate from the activities associated with this Committee. Just keep in mind that we are advisory to the Secretary of Health and Human Services. We don't advise the Congress.

I thank you for being very conscientious about these rules.

DR. TUCKSON: So the idea, by the way, which is important also -- I'm not going to keep embarrassing the new members, but just a reminder to everybody -- is this idea of we are advisory to the Secretary. So as you start to think about what we can do, think about the multiple roles of the Secretary of Health. Those multiple roles are, clearly, in terms of the responsibility for the CEO of all those agencies, but also of course the Secretary has a bully pulpit role.

But our recommendations, though, are within that framework. We are not able, as we have heard, to go out and tell the Congress what to do, even though we think we know. So be careful there.

The other thing is that I want to make sure that we as a Committee are attentive to each other and the hats that we all wear. The reason that you all are on this Committee is because of your expertise and because of the places from which you arise. It is a very considered process to get people from industry here, from academia here, from the genetic counseling community here, from government here, from the payers here. I mean, people are from many different places.

Everyone knows who you are, and people know and they are following this discussion. So you are free to let people know what you think. Let them know where you are and where you are coming from. Conflicts of interest we will always be attentive to and we will be monitoring them. We have all kind of people who are monitoring those sorts of things.

But at the end of the day, you are who you are and you bring your expertise to bear. You shouldn't be shy about that. I just want to make sure that you are comfortable. You are picked because of who you are.

One of the main goals of this meeting is to finish the important work we have been doing on pharmacogenomics. We have allotted most of our agenda today to a review of the final draft recommendations. We need to come to closure on them, and also determine whether we are satisfied with the content of the final draft report.

The materials for our discussion today are in Tab 3 in your briefing book. So we are going to go through those.

Before I turn to our leader, Kevin FitzGerald, to lead this discussion, I want to express the Committee's appreciation to you, Kevin, for your leadership and your dedication in guiding the development of the report.

I also want to thank Emily Winn-Deen, who chaired the taskforce during her appointment to SACGHS. Emily, you were instrumental in conceptualizing our approach to this issue and getting the initial work off the ground.

I also want to thank all the members of the taskforce, whom Kevin will name in a moment, for their time and effort and many contributions.

Sandra Howard, from the Office of the Assistant Secretary for Planning and Evaluation, deserves our gratitude for providing additional resources for the report's

development and in particular the excellent services of Cliff Goodman of the Lewin Group and his team of crack policy analysts.

Last, but by no means least, I want to applaud Suzanne Goodwin of our staff for her excellent work as the staff lead on this project. Anybody who has worked with Suzanne will know that she is a tough, tough taskmaster and she intimidates all of us. So we are grateful for you and your high standards, hard work, and commitment to excellence.

So we are going to go through this in an orderly way, folks. We are going to have a good, far-ranging discussion, but you are going to stay on point because, at the end of the day, we are going to bring this thing in on time today.

Kevin, take us through it.

DR. FITZGERALD: Thank you very much, Reed. Following up on what Sarah was telling us, I have to make an announcement that I have a significant personal interest in getting this done today. So I have a little bit of a conflict here. If this doesn't get finished today, my personal well-being will probably be at stake. During the break, if any of you want to see the psychological scars that I have received sitting here between Suzanne and Reed, I would be happy to make those manifest.

In any case, what I would like to do right now is give you a little bit of a history and an overview of the report, where we have been, what has gone on to bring us to this day. As you can see on our first slide, indeed as we reiterate what Reed has said, we are all about the finalization of this report.

The "we" of course is significantly dependent upon the taskforce. Now, it is not exactly a village. It is more like an extended family. As an extended family, we were very open and frank with one another, and that is how we got to where we are. As you can see, it is a great group. We had Jim Evans, Andrea, Julio, and Steve from the Committee itself, and of course, everything was begun by Emily. I too would like to thank her. She got the ball rolling. All I did was let it run me over and hang on.

I would also like to thank very much the input that we had from our HHS representatives, Gurvaneet, Muin, Steve, Liz, Alan, Greg, and Rochelle. Without their input, this report would be nowhere. We really did rely a great deal on their expertise and insight.

At the end of today, I will do a few more acknowledgements of the people who were instrumental in getting us where we are today.

How did we get here. Well, we began with some informational sessions which gave us the direction and the goal for the report. The first thing we had to do subsequent to that was a compilation of all the activities that were already ongoing. This is not something that we initiated out of thin air. As the report from the Secretary indicates, this has been building for some time and is now really taking on a great deal of momentum.

To get a good sense of that momentum, we also did a review of the literature to see the different perspectives that are out there, particularly to try and pick up the concerns that different experts from different perspectives have about how to move ahead with the idea of pharmacogenomics.

This led to the development and the revisions of a draft report. In that draft report, we came up with a certain number of recommendations. We then sent that draft report out to be reviewed by some experts that had been identified as people who could give us a more

comprehensive sense of where our report was situated at that time in the thinking about pharmacogenomics.

In response, we then did a few more revisions and then sent it out for public comment. What I would like to do now is give you a better sense of that public comment process.

The public comment period was from March 23rd to June 1st. Again, as you can see, ample time for people to get a hold of the report, take a look at it, and give us their responses. To facilitate that process, there was a directed targeting of some people.

As you can see, after the March 23rd announcement, it was put on the website but it was also put on the SACGHS listserv, which totals 936 different addresses. In addition to that, there was a "Dear Colleague" mailing to an additional 283 addresses. And then finally, some specific requests to organization membership, and that was about 31 different organizations. So we really did attempt to get a broad and deep response from people because of the significance we feel of this report.

In this slide, we tried to break down for you a sense of the terrain of the responses. Now, one thing I would like to point out here, it does say at the bottom the total is 57. That is not 57 individuals. That is 57 different compilation responses that we received. If you look at the public responses, many came from multiple individuals or from entire institutions or organizations, as you can see, so obviously representing the thought of multiple people within one response.

As you break down those public comments, you can see in our little pie chart, four were from government, 10 came from companies, 18 from organizations, and the largest group from groups of individuals or individuals themselves.

On the right just gives you some of the idea of the specifics of those subgroups. So from the government, you have NIH, OCR, Veterans Administration, companies such as Abbott, Amgen, Eli Lilly, Genzyme, GSK, and Pfizer. The organizations, a whole list of acronyms there. This is Washington, D.C. You don't exist if you don't have an acronym. So we met all of those. And then at the end, the individuals that were covered came from academia, healthcare providers, researchers, et cetera.

What was in the comments. It really ran the gamut. It covered a broad spectrum of concerns and suggestions, and some were fairly focused, looking at the text itself and offering corrections to inaccurate statements, inaccurate data, or data we needed to update; update of various activities that were ongoing about which we were not aware; and also, general ideas on how we might improve the report overall.

Then there were also comments on the recommendations, that area that most people take a look at when they look at one of these reports. So as far as modifications to existing recommendations, thoughts about which recommendations we should prioritize over others, and finally, whole areas that we had not considered. So, new recommendations that we thought about adding to the report.

That was the sense of the overview of these public comments. Now to give you some more specifics just so you get a feel for some of the content itself.

One of the comments that we heard more than once was that the report was somewhat overly optimistic about the long-term potential of pharmacogenomics. That certainly was not our desire. It doesn't do any good to put something out that isn't an honest, realistic

appraisal of where things are and where things might go. So we took that very seriously and wanted to in fact make sure that the report as it goes out is the best that we can do to give people a sense of the terrain and the possibilities.

It was suggested that we need greater discussion of the international efforts that are ongoing. Obviously, we are advising the Secretary of the Department of Health and Human Services in the United States. However, when one looks to see what decisions one might make certainly on a policy level, one always wants to know what is going on elsewhere just to get a little compare and contrast. So that was beefed up and we looked more in detail at some of the collaborations that were going on internationally and also in a public-private venue.

This raises the question of whether our conceptualization, our definition of pharmacogenomics, is adequate. I think it is a moving target. I certainly do not want to claim that what we are going to put out in our report is going to remain true for all time, but we certainly hope that it provides a platform for the Secretary to move ahead.

Also mentioned several times was the desire for SACGHS to address oversight of genetic tests. As you know, we are responding to that desire in an entirely different report.

There were some more focused suggestions. A call for the federal government to encourage collection of DNA samples in clinical trials to facilitate pharmacogenomics research. This is addressed in the report.

Need criteria to define what pharmacogenomics information should be included in a drug label. Obviously, another important aspect.

More emphasis on the need for more clinical effectiveness evidence to secure payer reimbursement. Call for value-based approach to reimbursement of pharmacogenomics products.

Interestingly, a disagreement within the comments we received about whether pharmacogenomics will necessitate genetic counseling. So again, something we attempt to wrestle with in the report, not necessarily saying that it is going to come out one way or another because we can't predict exactly how things will go in the future. But certainly, an issue that needs to be continually revisited.

We received, as you saw from the timeline before, the full set of comments in June of 2007. Each of the taskforce members was assigned eight comments to review so that we would get two people on each comment and then hopefully get a little bit of variety of opinion from our own taskforce members. Then the staff, i.e. Suzanne, reviewed all 57 public comments. After the therapy, she seems to be doing okay.

[Laughter.]

DR. FITZGERALD: In our review of all the public comments, we tried to answer a series of direct questions. First of all, looking at the comments that one had to address, which should be in the next draft of the report. In other words, should something actually be changed in response to a particular comment.

Of the comments that should be addressed, which would require the entire taskforce to discuss or which could just be addressed directly by staff. Primarily, the updates were something that could be directly addressed by the staff because that was just putting in the new information. So that was one of the examples for how we would take something and not necessarily bring it to the entire taskforce.

Of those that warranted discussion by the entire taskforce, how then did the

taskforce see we should go ahead with those comments.

How did we do this logistically. We had conference calls. Long conference calls. Two long conference calls. Both T-W-O and T-O-O. One was October 16th and one was September 10th, and if any of you have done these three-hour conference calls, you know after a while you are practically worried about having to have the phone surgically removed from your ear.

But in any case, a lot was done. We reviewed the discussion guide compiled by the staff. The comments were organized by the sections, as you will see, as the report is structured. And then action was taken upon the recommendations of the taskforce, primarily focused by the members who responded to a particular comment and also by then the comments of the taskforce members as a whole.

So we discussed the items. We flagged the ones that we had to discuss as a whole, and then we just made decisions about whether and how to incorporate those comments into the report.

I will mention this, too, at the end, and Reed has already mentioned it. There are, as with many of these things, people behind the scenes without whom nothing like this would get done. Again, the Lewin Group's staff has been fantastic. They have just been absolutely cooperative. They have been professional and also have responded well to intense psychological pressure. A very handy thing to note for the future.

So in collaboration with them, the report was revised and the recommendations were revised, and then we went forward with that. The revised report is in the briefing books under Tab 3.

So as we have heard already several times and we wanted to reiterate once again, the goal of today's session is to finalize the recommendations. We need to get even the wordsmithing done so we know what is going to move forward from here. This is what the Committee needs to vote on.

Now, if anyone, again, has specific editorial suggestions to the report itself, we would be very happy to hear those and receive those. Those we don't necessarily need to address today. Those can be incorporated in a continual editing process that will go on after this meeting. So I would recommend, if you have anything specific in the report itself, the body of the report, that you somehow indicate what that change would be and please give that to Suzanne so that we can compile those and look to see how they can be incorporated into the report.

Our focus today is on the recommendations. We need to get the wording down for all of them so that we can go forward with those.

Why do we need to do that today. Because after this we pull together everything so that in December the Committee members can see the final report, what exactly is going to go to the Secretary. Then that report will be copy-edited and made camera ready and then printed. Finally, in February, we target that time to send the report to the Secretary so the Secretary's Office, as we all know, has a month to look over the report and all and respond and then release it to the public, hopefully within a month. That is where we hope to be able to go in the immediate future.

So my understanding is everybody is to get a break before we get into the report, or no? You want to keep going? Should we get started? All right.

See, this is the way it is. Every time I suggested a break, Reed would say, "No.

Go, go."

[Laughter.]

DR. FITZGERALD: All right. Forward we go. The organization of the report. As you noticed, as we mentioned before, the report is in Tab 3 of your books. I believe, due to a specific recommendation from Andrea in one of our early meetings, the report -- we all agreed -- was organized into three overarching themes. These were areas where we thought important aspects of pharmacogenomics could be broken out into subgroups and addressed in a way that would allow us to keep contained within that subgroup our comments and yet, at the same time, make them into an integrated whole, which the whole report is supposed to be.

So the three overarching themes were research and development, the gatekeepers that are responsible for moving pharmacogenomics ahead, and then of course implementation of pharmacogenomics to improve outcomes in clinical and public health practice.

It would be impossible for me to overstate that third piece and the focus there, to improve outcomes in clinical and public health practice. This is something again and again to which we return. This is the goal. This is where we hope and we think the good of pharmacogenomics can go.

There are 15 recommendations. But of course, remember your college exams and the professor says, "There will be one question on the exam"? They don't tell you it will have eight subparts. Well, we have 15 recommendations and only 37 subparts. That is not so bad.

This is the first significant section of the report, research and development. This broke down into even further areas of focus. Obviously, basic research; what are the issues that are raised in that area. Then, of course, moving from basic research to clinical research and translational research overall. Raising, of course, the questions how then does one build an infrastructure that will enable and facilitate this research. Finally, the ethical, social, and legal issues that come up in research and development.

One thing you will notice as we go through the report is that the ELSI issues are raised in each of the three sections. Of course, we could have had an ELSI section, but we thought that it was better this way because we wanted to address those issues as they came along as we looked at these other subsections.

Looking at the second section, we talk about the gatekeepers, those who we identified, and others helped us identify, as the individuals critical to moving pharmacogenomics into the public sphere, getting it to those improved clinical and public health outcomes.

The four groups that were identified: industry, FDA, CMS and other third party payers, and of course, clinical practice guideline developers, professional societies in particular.

Now, if you will notice one thing here, before I said we had eight recommendations to that first section. Here we only have one. That doesn't mean that this subsection somehow is of less importance. But as I mentioned, these are the gatekeepers. This is the bottleneck, in a sense. Since you are only talking about the bottleneck, you only need one recommendation for the bottleneck: how to make it work better.

Finally then, we get to the third section. Again, this is the section that really focuses on where we hope pharmacogenomics can ultimately go. The implementation to improve outcomes in clinical and public health practice. This will involve several aspects that we need to address: education and guidance; information technology in pharmacogenomics; economic implications of pharmacogenomics; ethical, legal, and social issues in clinical

implementation of pharmacogenomics; and coordination of Health and Human Services pharmacogenomics activities.

One of the difficulties in any of these reports is being able to draw clear lines of distinction. It is virtually impossible. However, I think what one can do is try to identify foci from which one then looks out at the broader picture. So granted, education and guidance, information technology, economic implications, and coordination of activities within HHS are going to be relevant to all kinds of different issues we address: large population studies and oversight of genetic testing.

What we tried to do here is to situate some of those broader issues within the context or the focus of pharmacogenomics. We intentionally took this into consideration: parts of this report will in fact, hopefully, overlap well or coordinate well with earlier reports, like large population studies, and certainly subsequent reports, like the oversight of genetic testing. So we have tried to, in that way, formulate this report so that it is part of a continuum of the work of SACGHS.

You will see in this section we have Recommendations 10 through 15, with 16 subparts.

I hope that gives you a sense of how the report was structured and how we think, in any case, the report can best address the issue of pharmacogenomics.

What are we going to do today. We are going to stop now and listen to Reed.

DR. TUCKSON: Given now that I think we are getting ready to get into the discussion of the report itself, what we will do is we will take the break now for a second. That way we won't interrupt the discussion. Then we just plow right through it.

So here is the challenge. This is what I will call out for the new folks. We don't fool around with these breaks. I mean, I don't. So we start exactly when we say we are going to start. We do what we say we are going to do. Gurvaneet, you know that.

By the way, Robinsue Frohboese, we have read into the record all manner of incredible things about you, and I want to just say to you that we are very proud of the honor that you received, the highest award that your division gives out. You are terrific, and you are great on this Committee, and we think you are wonderful. So anyway, a round of applause for Robinsue.

[Applause.]

DR. TUCKSON: Now she will beat me up at the break. So we are going to start at 20 of. That gives you the 15 minutes. So we start at 20 of with the discussion. If you are late, oh my god, the woe that will befall you.

[Break.]

DR. TUCKSON: We are going to resume. We are going to now get to the discussion of the recommendations of the report. So if you all will take your seats, we will now begin with going through the report itself. Take it away, Kevin.

DR. FITZGERALD: All right. Thank you again, Reed.

Let me begin by just trying to focus our responses to the recommendations as we go through the report. So for each section of the report, we are going to review the key issues that we thought important to make clear. Then we are going to look at the current language of draft recommendations. So the emphasis here is on "current." Nothing is written in stone.

However, if you wish to change the language, you have to write the changes in

blood. I just want you to know it is going to cost you. No. We certainly are open and encourage all improvements to the language of the recommendations.

Now, Suzanne is going to do this real time. So as we are making the recommendations, you will see them up on the screen, and you will also have what is in your books so we can do compare and contrast as we move along. The idea is that we will get these recommendations to where we want them to be.

Then, at the end, when we have done all the recommendations and all the subparts, that is when we will vote on them as a group. Why don't we vote on them as we go along? Because we may do something later on in a subsequent recommendation that makes us rethink the wording we used previously. So I want you to know that that all remains flexible. As we go along, if you want to go back and revisit something, you have something pertinent from a change we made subsequently, we can do that.

Then, at the end, the idea is we will take them all as a package and say this is what we want to put forward as our recommendation. If we have time subsequent to that, we can look at some other aspects, but that is only if we have time subsequent to that. The key today is to get those recommendations well structured and clarified.

As we are looking at the recommendations, things we want to keep in mind. Obviously, as we heard before, we are here as an advisory body to the Secretary. So, are these the recommendations we want to make to the Secretary. Are these recommendations the best way to address the opportunities and challenges that we raise in the report. And of course, if you are not satisfied with the wording of the recommendations, what changes do you suggest.

All right. The first section, Research and Development. As I mentioned before, it had the subparts Basic Research, Clinical, Translational, Infrastructure. Again, we are in Washington, D.C. so everything is acronyms, but sometimes it is good to know what the acronyms stand for. ELSI, of course, is the short way of saying ESLI, which is the acronym for Ethical, Social, and Legal Issues. So it is not the name of my cow, or "Eslie." Right. Exactly. Since it is backwards here.

"Eslie," "Elsie," right. "Isle." Oh, I never thought of that one. There we go. Issues in Legal, Social, and Ethics, or something like that. But in any case, however you want to put the acronym together, those are the issues that are to be addressed.

Let's begin with basic research. In the report, what we identified is that more basic research is required. That basic research needs to identify biochemical pathways and related biomarkers involved in drug metabolism and drug response, to refine and improve sensitivity of high throughput methods for detecting gene expression and drug response, and to look at gene loci specific variability in drug response. So as you can see here in the basic research, the focus is a great deal on what the response is going to be to particular drug therapy or drug intervention.

One example of a group looking at this kind of thing is the Genetic Association for Information Network. If you are wondering what that is, on page 24 of your report there is a small explanation of that. I don't want to go into that now, but you can follow along in the report as we go through it.

Moving from basic to translational, T1 translational research is performed to validate basic research findings and to apply that knowledge to development of pharmacogenomics products. So we are all familiar with translational research and what the

intent of that is. Obviously, this has to be a very important part of the entire pharmacogenomics project. Another example there is the Pharmacogenomics Research Network. You can find that on page 25 of the report.

Then, of course, moving from translational to clinical, one aspect that is discussed in the report and that we discussed and also saw a great deal in the literature is the hope, at any rate, that pharmacogenomics can enable smaller, more efficient clinical trials. How would this be done? By using the test results to screen out subjects more likely to experience adverse drug reactions and of course, conversely, identifying subjects more likely to respond well to a drug.

So the whole idea, again, is to use that basic science information and data that is gathered to bring it to clinical trials and a greater focus on avoiding harm and gaining the benefit.

Obviously, in order to do that, you have to have the pharmacogenomic tests. How do you test people to see how they are going to respond to these drugs. What incentives are there to develop these tests. One would be projected market utilization and expected return on investment. As we mentioned, obviously, if you can avoid adverse events and improve benefits from any kind of drug therapy, that presumably would have a better return on your investment.

This would lead to positive clinical impact for test results because you would have the contribution of genetics relative to other non-genetic factors. In other words, now bringing in DNA sequence as a way of improving on our overall health care, which of course obviously involves non-genetic aspects. And of course, as we have mentioned already, hopefully reducing the prevalence and the severity of adverse drug reactions.

Now, obviously, since we mentioned early on we want to take into consideration some of the economic and financial aspects involved, gene patents and licensing practices are something that need also to be addressed because this is very much a driver in the arena.

So if there is going to be a development of these pharmacogenomic tests, how then does one look to see this development working alongside current drug development. Will there be a co-development of pharmacogenomic drugs and diagnostics.

We discovered that there is some resistance by industry to this process, although, hopefully, this resistance is being addressed. Not that the resistance is a bad thing. It is a good thing because it helps us to focus on the issues and formulate, hopefully, good responses.

Some of the areas that underlie this resistance: concern about market segmentation. Obviously, if you can focus on the subgroup that is going to benefit from your particular therapeutic intervention, then that is going to give you a smaller target population. Then, of course, there is uncertainty about FDA regulation of co-developed products. How is that going to be done.

In order to address these things, we presume that that is going to require new collaborations between drug and diagnostic companies and coordination of the parallel development processes.

In all, this could result in an expedited FDA approval, also in fewer label changes, and perhaps, in the greater likelihood, for provider uptake. If you know better what the outcome is going to be of a particular drug intervention, then you would be more likely to want to use that since you would have a greater likelihood of benefit and a smaller likelihood of any adverse event.

Another aspect which is interesting which has come up in several venues is this idea that there is the possibility pharmacogenomics could actually rescue some drugs and

therapies that have been discarded because of the results that were found with them in clinical trials.

It could be the fact that in a broad population one only sees a very, very small change, whether that is small in reducing adverse events or small in creating a benefit. But that small change may actually be the fact that within the broad population there is a tiny subgroup that really does benefit, whereas most other people don't at all. So pharmacogenomics could help rescue drugs that have been found to be ineffective under our current trial process.

Then, of course, the post hoc analysis, the analysis done after these clinical drug trials, could distinguish this subset of good responders. This is at least something that is being considered as a potential benefit from pharmacogenomics.

Mara, please. Just push the white button.

MS. ASPINALL: Let me add, although I'm not sure it changes the recommendation, but just a comment on your comment that it may not necessarily be a very small piece of the population for which this is the case. It could be one for which there is a dramatic negative effect on a small piece of the population that it is critical that those come out.

I think in the report itself you talk about this, but I think it is important to link this to the comments on market segmentation because the idea that it could lead to a smaller market segmentation is one piece, but it could also lead to a creation of a market that otherwise did not exist. The two are close, but I think they are directly comparable.

DR. FITZGERALD: Right. Thank you. Actually, the focus at least we were looking at in our comments here today was on the resistances to the pharmacogenomics. Obviously, that would be an incentive. But you are absolutely right. Thank you.

So as we address these issues, one of the questions that came up was, well, let's see how we can perhaps delineate these incentives or these resistances, and this is one way in which we looked to do it. So as you mentioned, Mara, the testing does have the potential to improve the safety and efficacy of drugs already on the market even in a broad way. That would be a possibility.

So, what are the incentives for pursuing identification of these new indications. Obviously, if one still has a drug under patent, that would create a greater financial incentive. Obviously, that would be less if it is off patent. Again, if the adverse reactions are severe, then one has greater incentive to address rather than mild. Of course, if there are alternative treatments available, there is less incentive because one can just use a presumably equally effective alternate treatment. So we just wanted to clarify the spectrum on that issue.

Looking at these small target populations and where pharmacogenomics might identify some, it raises the issue of what if it is a very small target population. We already have special provisions for orphan drugs and for humanitarian use devices, and these could encourage the development of pharmacogenomic products targeted to small populations.

The difference in this distinction is in the threshold for how these devices or drugs might be categorized. For something to be an orphan drug, the target population needs to be under 200,000 people. However, something to be categorized as an orphan diagnostic currently, our understanding is it has to be under 4,000.

One question is, if we are talking about the co-development of diagnostics and drugs, is that difference going to make a difference. Is that going to be a problem. In other words, the orphan drug could be favored in its development over the companion diagnostic. Is

that going to be a problem. This too was raised in the report.

Moving from basic to translational, these were some of the issues that were raised in our investigation of pharmacogenomics. Obviously, the adoption of pharmacogenomic technologies will hinge upon evidence demonstrating the value of using these products both in clinical and public health practice. That is, as we mentioned at the beginning, the goal. Is this going to get us better clinical utility.

Also involved in this clinical utility will be the idea of cost effectiveness. At what point does the cost of a particular treatment begin to affect how it might actually be disseminated into the public, in spite of the fact that it might have significant clinical utility.

One of the major issues that we discovered, and this again, too, will run throughout the report; there just isn't sufficient evidence regarding the clinical utility of most pharmacogenomic products. In part, that is because we are early on in the pharmacogenomics process. In part, it is also that there hasn't necessarily been a lot of incentive to gather that evidence. That doesn't mean some groups aren't looking at it, but really, one of the things that we found was we didn't find sufficient incentive to produce this evidence, which of course is absolutely necessary if we are going to understand what the clinical utility of pharmacogenomics is to be.

Looking at the research and development infrastructure, pharmacogenomics research and development could benefit from sharing and linking of research and clinical databases, repositories and records. When looking at the report that was put out by the Secretary on personalized medicine, you find on the front of the report "The right treatment for the right person at the right time." Great. No one can argue with that. The question is, how does one get there.

One of the things that has become clear is in order to do that you have to have an inordinate amount of information and the ability to compare and contrast different data sets across different areas of infrastructure. How can these be better linked so that that sharing of information can occur.

There are significant challenges to this. There are IP concerns. There are variations in data formats. Electronic health records are still in very early stages of development. There are different funding streams for all these things as well as different stakeholders, different administrative protocols, and different organizational cultures.

All of these issues will need to be addressed for us to get the sort of information sharing that we think is going to be absolutely necessary for moving ahead with the benefits of pharmacogenomics. As I mentioned, even though these challenges are very real, there are areas and groups that are beginning to look at these challenges. We have this list down at the bottom here -- there is a longer list, certainly, in the report -- of projects that are already attempting to address these challenges.

To the ESLI, ILSE, or ELSI issues, all ethical, legal, and social in the research and development of pharmacogenomics, here are some of the issues. Obviously, many of these will be familiar to you, but again, it is important to bring these to the fore. Certainly, privacy and confidentiality concerns are associated with sharing genetic information.

If the only way this goes forward is that researchers and clinicians have a great deal of access to very individualized, personalized information, how will those persons be protected from any misuse of that information. There will be tradeoffs. More access, more risk.

So, how will we balance protection versus access and utility. This is one of the big issues that needs to be addressed.

Another that we discovered is that, currently, there are discrepancies between human subjects research regulations, especially for coded specimens. One example is the Common Rule versus the FDA regulations. If you want more specifics on that, you can look in the report on pages 51 and 52. That was another issue that we flagged as something that the Secretary could certainly help to have addressed.

Another area that has come up -- and this is not, again, just in the pharmacogenomics arena but certainly one that needs to be addressed within that arena -- is the concern that concepts like race and ethnicity might be involved in the development of pharmacogenomics in a way that is not beneficial and in fact instead leads to problems with greater healthcare disparities or even a confusion of exactly what biological categories are being addressed, versus more socioeconomic categories that are often used in our society. These issues also need to be flagged.

Finally, again, as we try to [look at this] from a variety of different perspectives, looking also from the perspective of industry, there are liability risks associated with questionable marketing claims, labeling omissions, or incorrect or misinterpreted test results. How will these areas of potential confusion and potential conflict be addressed in a way that everybody can move forward with the benefits of pharmacogenomics.

With that overview, we get at the draft recommendations. This is Draft Recommendation No. 1. It is on page 25 of your report.

At this point, I need to let you know that the wording you will see on these slides does not always match the wording that is in the report before you. Some changes have already been undertaken. However, as I said, we are here now to finalize. So what is on the slide, what you see on the screen, may vary from what is in your report.

This recommendation is on page 25. If you will notice, under No. 1 on the slide, you will not find two prepositions that are in your report. "Basic research on the biochemical pathways associated with drug metabolism and drug action." In the report it says "on the genes and gene variations." Up here we don't have that. "Involved in these pathways and on," in the report but not here, "the functions of those genes related to the safety and effectiveness of drug treatments.

That is Subpart 1 to Draft Recommendation No. 1. Please take a look at it. Any comments, questions, or suggestions? Are people happy with this? This is our first recommendation. "NIH should put more resources into 1) basic research on the biochemical pathways associated with drug metabolism and drug action, genes and gene variations involved in these pathways, and the functions of those genes related to the safety and effectiveness of drug treatments."

DR. TUCKSON: By the way, can we assume, Kevin, that what is on the board is the newest [version]?

DR. FITZGERALD: Yes. What is on the board is the newest version.

DR. TUCKSON: So that is the one we are working from.

DR. FITZGERALD: Right. We are going to work from what is on the screen, and any wordsmithing we do is going to be put up on the screen immediately so everybody can see it. At the end, hopefully we will have what we have there on the screen.

Yes.

DR. GUTTMACHER: A point of clarification, I guess, for the NIH. When we say "more resources," do we mean a higher level than currently or do we simply mean continue to put resources into? If it is a higher level, can you tell me what the level is currently?

DR. FITZGERALD: Right. Compared to what. Compared to.

DR. GUTTMACHER: But I don't know whether it is compared to or simply "more" means continue to put resources in.

DR. FITZGERALD: Right. To be particularly precise, I'm just going to pull up what is in the report. First of all, the "more" that is there -- I believe this is accurate. I just want to make sure -- does indicate "more" in the sense of increased. I cannot give you the exact level of what is there right now.

DR. GUTTMACHER: Probably because the NIH couldn't tell you.

[Laughter.]

DR. FITZGERALD: Suzanne knows, though, but she is not telling. No.

So the idea here was to say this needed to be an additional effort. That answers your question.

Yes, Paul.

MR. MILLER: The recommendation is asking for NIH to dedicate more resources. Is there a problem with asking Congress to appropriate more resources as opposed to NIH basically taking from its limited pot, moving the deck chairs around, as a zero sum gain?

DR. FITZGERALD: We can't recommend to Congress. If you want Sarah to tell you officially, but --

MR. MILLER: No, I understand. I just want to flag that. Basically, the report is saying preference this immediate need and pressure on NIH over other immediate needs on NIH, when really the issue, I think, goes back to Congress in terms of appropriating money. I guess, given where we are and given the limitations on the Advisory Committee, that is the way it has to be. Is that correct?

MS. CARR: I think what you are getting is maybe you want the recommendation to either call for the request for additional funding or do you want us to specify whether we are asking additional funding or you want NIH to adjust its current priorities and the NIH director and the institute directors to --

MR. MILLER: My preference would be that it would be coming out of additional funding and that it is hard for me, personally, or for the Committee to say pharmacogenomics deserves a higher priority than cancer research or whatever. I think that is an implicit issue within the recommendation.

DR. TUCKSON: So, are you saying basically that the NIH should have available more resources, or we advocate that NIH have more resources to put into?

MR. MILLER: That would be my preference. I don't know if NIH has a problem with more resources or not.

[Laughter.]

DR. GUTTMACHER: It is a problem we could learn to live with.

[Laughter.]

DR. FITZGERALD: So we have a change here. "NIH should be given more resources to put into."

MS. CARR: Alan, what about saying "NIH should seek additional resources"?

DR. GUTTMACHER: The Committee could recommend that the Secretary seek more resources, since we are recommending to the Secretary. The way to fudge it would be to say "More resources be made available" without exactly saying how. Everyone knows what that means. You have to go out and get them somehow.

MR. MILLER: Maybe the way to fudge it or to identify the issue would be "NIH is in need of additional resources to put into."

DR. GUTTMACHER: "To increase its efforts in the areas of." Something like that.

DR. AMOS: Would it be appropriate to say something on the order of "The NIH should develop funding initiatives"? That is the process. You would actually develop an initiative with defined goals and objectives that would be submitted as part of your budget.

DR. WINN-DEEN: I guess it is my understanding that NIH prepares a budget request each year to give to Congress. So that is their opportunity to ask for what they need. That is, I think, where we were trying to get. They should define how much more resources they need and ask for those.

DR. FITZGERALD: Muin and then Julio.

DR. KHOURY: I guess this hasn't come up before, or has it, when there are recommendations from SACGHS going to the agencies. We would all like to have extra resources, whether it is NIH, CDC, FDA, et cetera. I'm not sure that we need to massage this one to death. But obviously, what needs to happen is the integration of genomics into all of these activities, from basic to translational. There could be a global statement at the beginning of the report rather than parsing out each one of these recommendations because they all require additional resources.

DR. FITZGERALD: And Julio.

DR. LICINO: Just one comment. Now it is pretty obvious that there is this time of very constrained resources, but even during the middle of the doubling when NIH did an initiative on pharmacogenomics, some institutes participated and others did not and chose not to. So I think that [we should] emphasize that it should be an area of importance with whatever budget you have. Of course we need new funds, but even when new funds have been made available in pretty large amounts, not everybody saw the need.

DR. FITZGERALD: Would people be comfortable with "NIH should receive and put more resources into"? That covers both. Alan?

DR. GUTTMACHER: Yes, I guess that would work.

DR. FITZGERALD: Thank you. Muin, no?

DR. KHOURY: Why do we have to say that? Because every single recommendation will have to say the same thing.

DR. TUCKSON: Why don't we just go through the rest of them, then. We have the spirit of this.

DR. FITZGERALD: We will put this down temporarily.

So, No. 2. First of all, is everybody happy with No. 1? We are just getting the sentence started here. Yes, Barry.

DR. STRAUBE: Barry Straube from CMS. As to the segment you have lifted out, "safety and effectiveness," which is the FDA statutory language, it is a victory, of course, as

the report mentioned, if we get something declared safe and effect by FDA but payers can't pay for it.

At CMS, "reasonable and necessary" is the term. "Medical necessity" gets mentioned in the report quite a bit. I think one of the weaknesses we have had over the years is that basic research looks at safety and effectiveness but it doesn't look at medical necessity and gather evidence as much as it might to make the payment structure be able to respond.

So I would suggest that this ought to include some mention of either "medical necessity" or "reasonable and necessary." We will be talking later on when you get to the FDA place about how we are trying to work with them.

DR. FITZGERALD: Right. We will be. Emily.

DR. WINN-DEEN: I think we were trying to differentiate the basic research, understanding the underlying science, from the kind of things you are talking about, which come later in our recommendations as we get more into the translational aspects of it. At that point, absolutely, we want to be looking at those things. But if you don't even understand the basic biology of how a drug is working, then it is hard to move to the next step.

I think that is what we tried to do. We tried to break this down into several subsets. The first thing you have to do is the basic, and then you do the translational and clinical. At the end you obviously want to have all of those measures -- good, sound science plus the health economics -- understood.

DR. STRAUBE: I understand the logic. I'm just suggesting that I can't tell you how many times we have many, many folks, including around this table, coming in and we are asking for information that if it had been thought about way back in the basic science phase, it could smooth the road. That's all.

DR. FITZGERALD: Let me just get the sense of this. If we, at some point in one of these basic research recommendations, put that in, would that address it? Or would you want it in every one?

DR. STRAUBE: No, no. I'm just trying to sensitize the Committee.

DR. FITZGERALD: Actually, the next one, No. 2, might actually have a spot where it would fit very nicely, if I can hold that off just a second.

DR. STRAUBE: Absolutely.

DR. FITZGERALD: Yes, Mara.

MS. ASPINALL: Just one question on No. 1. When it talks about drug treatments, later on you talk about diagnosis as well. Does this one need to, or can it, broaden itself to say "safety and effectiveness of drug treatments and diagnoses" or was this really meant to be just the work on the therapeutics and not to include basic research on the diagnostics?

DR. FITZGERALD: So we would put in "effectiveness of drug treatments and diagnostics"?

MS. ASPINALL: Or "diagnoses," yes.

DR. FITZGERALD: Anybody have any problem with that? It is just more inclusive.

[No response.]

DR. FITZGERALD: All right. So, "diagnostics," good. Any others on this?

[No response.]

DR. FITZGERALD: Great. Let's move on to the second one. If I miss anybody,

if your hand is up and I miss you, just throw something blunt and heavy. I will duck, but Reed will take it well.

[Laughter.]

DR. FITZGERALD: No. 2, put more resources into "Non-hypothesis-based approaches to the understanding of the relationship between genetic variation and individual's response to drugs." Yes. Please, Paul.

DR. BILLINGS: Could you give me a little background? I'm exercising Reed's admonishment for us new ad hoc types. Could you give me a little background on why this was included at all? It sort of sticks out, and I just wondered.

DR. FITZGERALD: Yes. Why don't you take it, because Emily can do this better than I.

DR. WINN-DEEN: The idea was that Recommendation No. 1 had a hypothesis-based approach that you are going to look at specific pathways, and we also wanted to include the fact that we don't always know. So we wanted to also open the possibility for non-hypothesis. Not assuming that you say a drug is working through this particular pathway and so we are only going to study that pathway but to look at more whole-genome kind of approaches to things.

DR. FITZGERALD: Anybody else on this?

[No response.]

DR. FITZGERALD: Great. All right. So we are going to keep that the way it is and move on the next recommendation, Draft Recommendation No. 2, which is on page 26 of your report. In this recommendation, what you have in your text differs from what is on the screen, and I will point out where.

"As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx tests and," is not in your book but it is on the screen, "tests and technologies and to assess their clinical validity and clinical utility."

Mary, this is where I thought maybe we could add something along the lines of what you were thinking.

Below that, "HHS agencies should facilitate the development of clinically useful pharmacogenomics technologies by investing more resources into all components of translational research, including the translation of basic research findings into clinical trials." That, I believe, is not in the text. The "S" is missing in the report.

"As well as the translation of clinical research findings into clinical and public health practice and policy. One of the emphases of this translational research should be to foster," and I believe that is not also in the text of the report, "to foster the development of more rapid, cost-effective genotyping technologies."

Rather than just say "should be the development," we have put in also "to foster the development."

Barry, does this get at more what you were [saying]?

DR. STRAUBE: It does somewhat.

DR. FITZGERALD: Could we make it stronger with your language?

DR. STRAUBE: I'm just wondering whether, since you used the language here of "into clinical and public health practice and policy," "policy" might entail coverage, but you

might want to put "coverage" in there also.

DR. FITZGERALD: We can put "into clinical and public health practice, policy, and coverage." Everybody comfortable with that? Great. Good.

Who am I missing? Sorry. Paul, go ahead. Thank you, Mara.

DR. BILLINGS: I'm going to exercise this role one more time. The recommendation recommends genotyping technologies when in fact phenotyping is probably, in many cases, closer to the clinical reality of changing practice. So, what was the background for the final sentence, really?

DR. FITZGERALD: Well, again, it is not a situation where this is being emphasized to the exclusion of the other. Up here on the slide it says "to foster the development of more rapid, cost-effective genotyping technologies focusing on the pharmacogenomics." Phenotyping technologies would be incredibly broad, in one sense. That could involve all sorts of biochemical areas. Jim.

DR. EVANS: This must have gone by me in one of the conference calls, too, because as you bring up here, I think that does kind of stick out. I'm not sure why we necessarily need to or should emphasize very specifically "more rapid genotyping technologies." I think the first sentence really sums up what we want to go get to, and I'm not sure we should be that specific there.

DR. WILLIAMS: Kevin?

DR. FITZGERALD: Yes.

DR. WILLIAMS: One way to address this might just be to, in that last sentence, strike "genotyping" and substitute "diagnostic."

DR. FITZGERALD: That is one way to go. This was a recommendation that was made specifically by one of our members, who is not here at the moment.

We can either get rid of the sentence or we can put in "diagnostics." Is "diagnostics" better? Yes, Gurvaneet.

DR. RANDHAWA: If we could just go back to the beginning of the paragraph where we say "PGx technologies," and just restate it "PGx technologies" down [at the bottom.] Instead of making it more specific, we could just say "PGx technologies."

DR. FITZGERALD: Rather than diagnostic. Jim, you don't have a mic. Hold on. It's coming.

DR. EVANS: Again, I think when one thinks about translational research, it is extraordinarily important at that level to think about a very broad range of things that includes, as is stated, clinical validity and clinical utility. This gets far beyond diagnostics. I think that "diagnostics or even "technologies" is too narrow. I think we should just knock out that last sentence. There is much more clinical utility than technology.

DR. FITZGERALD: What Jim is recommending is we just cut out that last sentence completely. Emily?

DR. WINN-DEEN: I guess I will just do the counterpoint to that: if you only develop the correlation but you don't have a good way to deliver that for patient care. I think that is what we were trying to achieve by adding that sentence.

DR. EVANS: Yes, but I think by singling out one aspect, be it technology, diagnostics, one loses the important general recommendation, which is to encourage a neglected facet, which is translational research. I think that a specific recommendation there that focuses

on technologies or that focuses on diagnostics runs the considerable risk of really punting it back to [the idea that] we need better genotyping platforms, which isn't translational research.

I would vote, and maybe it will come to a vote, for getting rid of that last sentence.

DR. FITZGERALD: Let's do it this way, I guess, first of all. We have two choices, it seems to me. One is getting rid of that last sentence and the other is somehow changing that last sentence.

Looking at that, is there anyone here who is against getting rid of the last sentence?

[No response.]

DR. FITZGERALD: So we could all live with that. Yet we have one person who doesn't really want to live with changing it even if it is changed. Why don't we, for right now, just get rid of that last sentence. Then, if we come back and say we need to be more specific later on, we can do that.

All right. Why don't you just delete it for now. Great. That solves that issue. Great.

Next is 3A, page 30. By the way, our crack mic technician is going to be crawling around. He should do whatever he needs to do because he is going to fix this and then we will be fine. So pay no attention to this person running around.

This particular recommendation is the same in both the report and on the screen. Again, on clinical research, Recommendation 3A, "Where study results will be used to demonstrate safety and efficacy to support a pre-market review application, sponsors and researchers should be encouraged to consult with FDA early in the study design phases. This would help to ensure that these studies have adequate clinical study design, e.g. sufficient statistical power, and quality controls in place should the research later be submitted for regulatory review."

Again, I think the idea was to get back at some of what Barry was talking about before, trying to look down the road and see if we can't pull these things more closely together.

Is your mic on yet? Yes, it is.

DR. STRAUBE: Again, I might suggest you put in FDA and CMS because, again, we are talking about parallel review at concept. I think that gets people in earlier.

DR. FITZGERALD: Sure. FDA and CMS. All right. Good. Any other suggestions or any other recommendations?

[No response.]

DR. FITZGERALD: Great. All right. We are going to move on, then, to 3B.

Now, again, this is different than what is in your text. We have "As appropriate" at the beginning of this recommendation. So, "As appropriate, NIH should consider making FDA's existing quality of evidence standards a component of their assessments of the scientific merits of grant and contract submissions."

Everybody is comfortable with that. Fantastic. All right. Great. On to the next, 3C.

"NIH should encourage grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program to ensure consistency in data standards that may affect drug prescribing."

Yes, Marc.

DR. WILLIAMS: I just had a question on this one. I'm sure there was debate about the word "encourage" versus "require." Given that NIH does have the ability to supply funds, it would be, as I understand it, within their purview to be able to require submission as part of the RFA. So tell me a little bit about why the word "encourage" was chosen as opposed to "require."

DR. FITZGERALD: You are absolutely right. That was discussed. My sense, and Suzanne's sense, of the discussion was that we leave it a voluntary program and not make it mandatory. [That] was something that was thought to be preferable.

DR. WILLIAMS: I would just note that it doesn't change the FDA's program from being voluntary, but for people that want to do research using NIH funding, there is nothing that would say that the NIH couldn't require it.

DR. FITZGERALD: Exactly. That is true. Alan.

DR. GUTTMACHER: I would just ask, if we did change it to "require," of whom should it be required? Every NIH grantee? I don't think so. You would have to add "As appropriate," I suspect, if you went from "encourage" to "require."

DR. FITZGERALD: Right. Is what you are saying, Marc; it should be of every NIH [grantee]? No.

DR. GUTTMACHER: I guess I would need clarification. There are certainly lots of NIH grants that have absolutely nothing to do with this area, so one would not require it of those grantees.

DR. WILLIAMS: Are you saying, Alan, that you would be comfortable if we say "NIH should require grantees and contractors as appropriate to participate"?

DR. GUTTMACHER: Yes, I think you could put the "as appropriate" any place in the sentence that you would like.

DR. WILLIAMS: That is the direction that I would favor, unless there are compelling reasons from the taskforce's discussion.

DR. FITZGERALD: Sylvia.

MS. AU: I think I would keep it as "encourage" because there might be some research done in special groups that would not be able to do the research if it was required of them to participate in the FDA Voluntary Genomic Data collection.

DR. FITZGERALD: Julio, did you want to [speak]? Your mic is on.

DR. LICINO: Yes. I think it is a very important thing because, if you make it optional, few people would deposit. I agree with Sylvia. But on the other hand, if you make it mandatory, it may affect some types of research. So it is a difficult one.

DR. FITZGERALD: This is basically where our discussion was.

DR. GUTTMACHER: That is where the "as appropriate" might work. It might be inappropriate to do it in situations where it would kill off the avenue of research.

DR. FITZGERALD: Let's get Paul and some other people. Joe.

DR. TELFAIR: I would use both "encourage" and then "as appropriate." Then you would encourage but it should be as appropriate. Here is the reason why: you still have to designate who would be responsible for monitoring whether or not that occurred. So, "as appropriate," it would go to the appropriate agency program, subprogram, et cetera, within the NIH and, I'm assuming, working with that. You would have to be able to do that. You wouldn't

just leave it wide open.

The same arguments that are being made for "mandatory" should also be considered as to who then would be responsible for even monitoring whether or not those that are encouraged to carry it out actually carried it out and then what to do with that.

DR. FITZGERALD: Great. Paul.

MR. MILLER: Just as a matter of wordsmithing, or maybe it is just a style issue, I'm uncomfortable with throwing in the fray the phrase "as appropriate" because I'm not quite sure what that means. I think it is a really wishy-washy term. To the extent that you want to limit this thing, either this or even the previous slide -- and I bit my tongue on the previous slide -- then we should state exactly what we mean. I think "as appropriate" is so ambiguous it tends to confuse rather than clarify. That is my opinion.

DR. FITZGERALD: I have Marc, Gurvaneet, and then Steve Gutman. Marc.

DR. WILLIAMS: Just to respond to Sylvia and to Paul, from Sylvia's perspective, I think that there could be an exemption process for research where this would be a barrier to actually doing the research. I think, to Paul's point, what we are really talking about here is perhaps some language that would encourage -- and I don't know who this would be within NIH -- to basically develop policy around who would be exempt, essentially, from submission and under what circumstances that exemption would be reviewed.

MR. MILLER: I think that is fair. If I could just respond, it may be that you place some language in the text of the report explaining that rather than putting it in the recommendation. That might be as appropriate as anything for that phrase.

[Laughter.]

DR. FITZGERALD: Gurvaneet.

DR. RANDHAWA: My comment was, as we go further in this field, AHRQ certainly is funding one randomized control trial on genetics in Warfarin use. I'm assuming CDC will also be funding grantees and contractors collecting genomic data. So, is it viable to consider other agencies beyond NIH who also fund, or hopefully will fund more, pharmacogenomics research to be in this recommendation?

DR. FITZGERALD: So now we are adding. Mike, go ahead.

DR. AMOS: Just to clarify, to Paul's point, it might be wise to just include the statement "When genomic data is generated in a study funded by NIH, then." You say can "required" or "encouraged"; it is up to you guys.

DR. FITZGERALD: That would give us our specificity. Yes, Muin. Go ahead.

DR. KHOURY: Isn't this clinical research arena relevant to the clinical research that is leading to a pharmacogenomic application to be put as a test or as a tool? There is all kinds of research. I think we have reached the point where we are at this interface of translation between after gene discovery for pathways or whatever and trying to develop an application that then could be submitted to the FDA.

So "when appropriate" can be massaged to [apply to] the funded research that is designed to evaluate or develop applications to be used for pharmacogenomic practice. The encouragement or the requirement would be for that kind of research to interface more with the FDA processes, whether it is funded by NIH, CDC, AHRQ, or whatever. I know we will be funding some, but I know most of the funding will come from NIH, that's for sure.

So, "when appropriate" is not really about all genetic research. It is only the

pharmacogenomic research that is leading to that application. It is probably a small fraction of the genetic research in drugs and development. We have reached a point in that translation pathway that is more distal and therefore more selective, so there could be some wordsmithing that goes along [with that.]

DR. FITZGERALD: That is what we are supposed to do. Right. So, smith away.

DR. KHOURY: So it is not really when genomic data are generated in a federally funded study. That is ridiculous because that involves hundreds and thousands of potential studies that will never make the light of day in terms of application.

So, when pharmacogenomic data are generated for the purpose of developing a pharmacogenomic application or test for use in practice, that is when the trigger happens. I'm sorry; I'm stumbling on my own words. Maybe others can help me here with the massaging.

DR. FITZGERALD: Steve, go ahead.

DR. GUTMAN: That is not entirely right because Voluntary Genomic Data Submissions are actually posited to look at the use of genomic data earlier in the life than at the point that a diagnostic device is poised to enter the market as a companion product. In fact, when a diagnostic device is poised to enter the market as a companion product, the Voluntary Genomic Data Submission process is the wrong process. You actually need to start thinking about the pre-IDE or the CDRH protocol review process.

If you are actually going to play around with the language, it is going to need to be parsed a little bit more cleverly than this. In the true exploration or feasibility stage, when you are playing around with genomic data in the context of the drug, the Voluntary Genomic Data Submission really hits the spot. When you have a companion diagnostic that looks like it is on the way, then you need to start thinking about a pre-IDE or a protocol review by the Center for Devices.

But I also agree with what Muin says that we better be careful what we wish for because we on FDA's end don't actually have the resources, depending on how generous NIH funding in this area is, to start looking at a lot.

I do think you need to step back, as ambiguous as it is, and put some kind of disclaimer in there, some kind of buffer. For one thing, the Voluntary Genomic Data Submission is an exploratory process, but as it gains experience it will start to create guidances and documents. It doesn't need to keep reinventing the wheel so that someone who comes along with a third model of a particular kind doesn't necessarily need to submit back to the Voluntary Genomic Data Submission because that route has been established.

I personally prefer allowing some kind of flexibility here, although I must say, I always thought that it would be really nice when you did have a new diagnostic product that NIH was funding that they require that they at least read FDA regulatory documents so they understand that research that is going to generate a product has certain obligations about quality control and following the protocol and doing things that may have a heightened exigency.

DR. FITZGERALD: So, for the VGDS, this Voluntary Genomic Data Submission Program, do you have wording that would fit that program for this recommendation? The mic is not on, Steve.

DR. GUTMAN: Let me see. So it would be, "Should participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug

development." No, after "Voluntary Genomic Data Submission" would be "the exploratory phase of drug development and the pre-IDE process when a diagnostic is thought to be essential in the clinical use of the drug."

That is a demarcation between the Voluntary Genomic Data Submission and the pre-IDE. In the Voluntary Genomic Data Submission, you may be in true genomic discovery and you are not sure about the need for a drug, or you may suddenly get that you need a diagnostic. When you know that you are going to need both of them to enter the marketplace as bride and groom, we are the wedding hall.

DR. FITZGERALD: We are still smithing here.

[Pause]

DR. FITZGERALD: Do we want to go back to "HHS should encourage" or "require"? "HHS should require grantees, as appropriate, to participate in FDA's Voluntary Genomic Data Submission during the exploratory phase of drug development as well as the pre-IDE review process." So, Steve, what comes after the "pre-IDE review process"?

DR. GUTMAN: "In situations where a diagnostic is thought to be essential to drug use" or "clinical drug use."

DR. FITZGERALD: "Essential to clinical drug use." I'm sorry. Scott. Sorry.

LT. COL. McLEAN: The language of "requiring" participation in a voluntary activity is kind of a wordsmithing issue.

[Laughter.]

DR. WILLIAMS: It is really not because, as I pointed out before, anybody can submit to that voluntary program that wants to. But what I'm saying is you are getting money from an HHS program, then you have to. That is completely consistent syntactically and semantically and any other way that you want to look at it. If you are getting money from somebody, they can require you to do something that might otherwise be voluntary.

DR. FITZGERALD: Yes, Paul.

DR. BILLINGS: I have a point and then a question. First of all, there are two Pauls now here. I would like to be referred to as "Paul the Lesser" and "Paul the Greater" next to me here, and "Paul the Wiser."

[Laughter.]

DR. BILLINGS: So, "Paul the Lesser," please, from now on.

Second of all, I'm a little confused. Segmentation can occur very early on either in the pre-clinical phase or in contemplation of the clinical phase of drug development. That segmentation in the contemplation of the collection of data may have nothing to do at the end with any labeling recommendation or so forth.

So I'm a little confused at this language as to how that is dealt with. I don't have a recommendation how to improve it. Steve just said in my ear a minute ago maybe you put "or" in the pre-IDE review process, because that would then cover people contemplating clinical trials but then not actually deciding that they want to submit with the segmentation data.

DR. FITZGERALD: This is what we have currently. "HHS should require grantees and contractors, as appropriate, to participate in FDA's Voluntary Genomic Data Submission Program," which may shortly be renamed to the Semi-Voluntary. No. "During the exploratory phase of drug development or the pre-IDE review process in situations where diagnostics are thought to be essential to clinical drug use."

One way to maybe wordsmith it just a little more is remove "as appropriate" since we are already saying what the conditions are at the end.

Jim.

DR. EVANS: Not withstanding Marc's comments, which are technically correct, I think leaving "requirement" and "voluntary" in there is going to create incredible confusion. I don't think there would be any problem with just getting rid of "voluntary." It is still a program and we could say, if everyone feels it should be a requirement, that they are required to participate in the Genomic Data Submission Program.

While you are right technically, I think there will be a lot of confusion.

DR. FITZGERALD: Wait a minute. Use the mic so we can get this all down. I have Andrea, and then Steve, did you want to get back in the game?

DR. FERREIRA-GONZALEZ: The name of the program is "Voluntary." I don't think we can change it.

DR. FITZGERALD: We could always use the acronym. Then people wouldn't have a clue what it is.

[Laughter.]

PARTICIPANT: I think it would be very odd to take "voluntary" out.

DR. FITZGERALD: Marc, go ahead.

DR. WILLIAMS: I want to come back to, I think, the point Paul Miller, or whatever "Paul" we are referring to him as now, [made.] Reference within the recommendation that the Secretary will convene the relevant HHS agencies to produce -- and I don't know whether these would be rules or regs or policies or whatever -- to address the specific circumstances under which this requirement would be active.

DR. FITZGERALD: Do you want that in the recommendation or do you want that in the text?

DR. WILLIAMS: I think it needs to be expanded in the text, but we are making recommendations to the Secretary so it has to be in the recommendation as well as in the text.

DR. FITZGERALD: "Convene the appropriate agencies to address implementation of this recommendation."

Marc, just to remind you and everyone again, that is why we are voting on these at the end. There is Recommendation 15A, which is a recommendation to say that an interdepartmental workgroup should be established to review all the recs to implement them. So 15A is sort of a grab-bag, trying to get at what you just said, but for all the recommendations. Is that okay?

DR. WILLIAMS: What you could do, then, is you could just basically say that "Implementation of this recommendation will be addressed per Recommendation 15A," something like that.

DR. FITZGERALD: Let's give Suzanne a moment here to get this together. Any other comments? Steve, please.

DR. GUTMAN: I would change the "or" to "and/or" because there might be circumstances where both processes are appropriate.

DR. FITZGERALD: Let her get the other one in there and then we will do that. Then, "and/or" rather than "or" in front of "IDE." There we go.

No, we didn't take out "voluntary." We are just going to use the acronym so no

one knows what it is.

[Laughter.]

DR. FITZGERALD: "HHS should require grantees and contractors to participate in FDA's VGDS Program during the exploratory phase of drug development and/or the pre-IDE review process in situations where pharmacogenomic diagnostics are thought to be essential to clinical drug use. Implementation of this recommendation will be addressed in Recommendation 15A."

I'm sorry. Muin.

DR. KHOURY: Again, since you said that implementation of all the recommendations are going to be addressed in 15A, it seems a bit redundant to have that. Marc, with apologies to you, everything will have to be implemented in an orderly process with HHS agencies coming together. So just to single this one out seems a little bit odd to me.

DR. FITZGERALD: Would it be adequate to have asterisks? Looking ahead, we may have other recommendations we want to make sure relate to 15A. We could just put an asterisk. We just want to emphasize that it relates to 15A. We don't need it? No? All right.

All those who think we don't need this, pick up your glasses and throw them at Marc. No, no, no.

[Laughter.]

DR. FITZGERALD: Are you okay, Marc, with that? Hopefully it will fall under 15A. Presumably it will.

All right. How are we with the language, though, right now? "HHS should require grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program." If we just can't bring the public to greater clarity in the use of the English language, what good are we, right? All right. "During the exploratory phase of drug development and/or the pre-IDE review process in situations where pharmacogenomic diagnostics are thought to be" -- wait a minute. It is changing again. "Are thought to be essential to clinical drug use."

What did we change? What did you just change? "Its grantees," okay. Wait a minute. Get your mic, Sarah.

MS. CARR: It is just a small point. The "in situations" applies to both of the two. What if you began the recommendation with that phrase? Would that make it easier to follow?

DR. FITZGERALD: I see. The suggestion is to move that phrase to the front because it applies both to the VGDS and the pre-IDE. Okay? Okay. Move that to the front. Thank you, Sarah.

I'm sorry, Paul. Paul the Lesser. First is "Paul the More."

DR. BILLINGS: Paul the Greater and Paul the Lesser.

DR. FITZGERALD: Whether it is "additional" or whatever, but it is "more."

DR. BILLINGS: Exactly.

[Laughter.]

DR. BILLINGS: During the discussion of this recommendation, was there some consideration of what is going on in the drug industry and the non-grantee population and how there might be some harmonization of what is going on in the non-grantee world and in the grantee world?

DR. FITZGERALD: Yes, that was part of our discussion around this. It was part

of why it was "encourage," I think, rather than "require," also. Are you suggesting --

DR. BILLINGS: I don't think it serves the purpose of this Committee to set up two parallels since they have two systems that don't really talk to each other. It doesn't serve the public interest either, by the way.

Now, I recognize that there are barriers, some important ones, but that doesn't mean that we can't recommend better harmonization or sharing of data or ways that that would happen.

DR. FITZGERALD: We do have that in the recommendations. Let me just make sure. I think it is further on when we talk about the information.

Marc, you wanted to say something.

DR. WILLIAMS: Again, I think it is just a matter of making sure that as we look at each of these recommendations that we understand what our Committee can actually do. We can only recommend to the Secretary, and the Secretary has no ability outside of monies that HHS controls that they may distribute to private entities to really compel them to do anything.

In the text of the report there is a lot of verbiage as to why it is important that there be communication, that there be consistency, and that we have, as needed, parallel pathways. But beyond encouraging the voluntary participation, there is not much else that can be done in the context of the actual recommendation.

DR. FITZGERALD: One second, Paul. Emily, then we will get back to you. Go ahead.

DR. WINN-DEEN: By taking the data format that has already been vetted with the PhRMA side and now asking the federally funded researchers to use that same format, the idea was that those things then would be more translatable across both the privately funded research as well as the public, rather than having the public set up a whole separate database structure and everything.

So there was method to the madness of choosing the FDA Voluntary Data Submission round.

DR. BILLINGS: Certainly, the text of that should be clear so that when the PhRMA folks read this they can get the idea of what we were getting at.

DR. FITZGERALD: Do me a favor. Take a look at the text. If you could see a place to put that, that would be great. Get that to Suzanne. Just to point out to you, when we get to 6A we are going to address this also with the industry.

So we have, "In situations where pharmacogenomic diagnostics are thought to be essential to clinical drug use, HHS should require its grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development and/or the pre-IDE review process."

Going once, going twice, sold. All right.

MS. ASPINALL: Paul the Greater has something to say.

DR. FITZGERALD: Paul the Invisible. No.

[Laughter.]

MR. MILLER: What do you mean by "are thought to be"? "Are thought to be" by whom? Why not just "diagnostics are essential"?

DR. FITZGERALD: So you want "diagnostics are essential"?

MR. MILLER: Yes.

DR. WINN-DEEN: I think you are still in the hypothesis stage.

DR. FITZGERALD: They are not always, so there is our problem. But, "may be essential."

DR. WILLIAMS: But I know where Paul is coming from because, if somebody says "Well, I don't think they are," that can be used. We need to be adequately explicit about what we mean and avoid the weasel words where people can kind of get around.

MS. ASPINALL: How about have the --

DR. FITZGERALD: Wait a minute. We have already here "In situations where," right? So, in a situation where pharmacogenomic diagnostics are essential. It is the situations that count. That has to be designated by somebody. That's fine. It doesn't have to be in situations that are thought to be. It is just in situations where, and then someone has to designate what those situations are. Is that okay? Okay.

MS. ASPINALL: You may have resolved it with doing that, but I agree with getting rid of "are thought to be." I think the question is, at what point do you know they are essential. That is the key issue.

DR. FITZGERALD: That will have to be determined. That is Recommendation 15A.

MS. ASPINALL: I'm there.

DR. FITZGERALD: So now we have, "In situations where pharmacogenomic diagnostics are essential to clinical drug use," and then from there. You didn't change anything else, right? Okay.

All right. I look around. Going once, twice, three times, sold. Next.

Remember we can come back and revisit these if new thing come along, but let's keep moving. Until we vote on it, nothing is ultimately, truly, concretely final. Unless we don't get to a vote.

This is for your information. This will not be in the recommendation, but we just wanted to flag some of the recommendations that came from the public comments. This was one of them.

"HHS should enable the investigation of biomarkers associated with drug response by encouraging sponsors of federally funded clinical drug trials to request appropriate biological samples from research participants." Marc? No. Mara, please.

MS. ASPINALL: Maybe it is implied, but it seems to stop a little short of doing something with those samples. When it says to request samples and get the appropriate permissions for relevant testing?

DR. FITZGERALD: In other words, they would have to be done with informed consent and all that sort of thing, right? I'm presuming.

MS. ASPINALL: And something has to be done with them, as opposed to just getting the samples. So maybe the thought is it is implied and it is in the text, but it seems to me that it was missing the second half, which is we are not just getting samples for samples, we are getting samples to be used --

DR. FITZGERALD: Biomarker-associated drug response research.

MS. ASPINALL: Yes.

PARTICIPANT: You could say something like "to facilitate pharmacogenomic or biomarker research."

DR. FITZGERALD: I think the first part says "HHS should enable the investigation of biomarkers associated with drug response." I thought that was the target?

MS. ASPINALL: Is that enough?

DR. FITZGERALD: But, is that not clear? We could rotate things around. We could put that in the end if you want to do it that way.

MS. ASPINALL: That, to me, makes more sense because you could just say "enabling" in the broadest way and they are requesting samples from the research participants and they are done. From a public comment [standpoint], as people get more concerned about requesting samples from participants, I think it is important to connect it with what is going to be done with those samples.

DR. FITZGERALD: So, "HHS should encourage sponsors of federally funded clinical drug trials to request appropriate," "in order to enable the investigation of biomarkers"?

MS. ASPINALL: Maybe the other way. "In order to encourage the investigation around biomarkers, HHS should encourage sponsors of trials to request the appropriate samples and" -- I lost myself here. I would add "and get the appropriate permissions for" --

DR. FITZGERALD: I think informed consent and all that would obviously be implied. They are not going to do anything that is. They better not, anyway.

MS. ASPINALL: Because, again, that would be relevant to all the recommendations.

DR. FITZGERALD: Right. Exactly. Gurvaneet and then Michael.

DR. RANDHAWA: I'm just concerned we are getting bogged down with the granularity here. Comparing this recommendation with Draft Recommendation No. 2, which is so broad that you are facilitating all kinds of technologies by translating basic research and clinical trial into policy, in this recommendation we are just talking about access to some biological specimens in one situation only.

But this is a larger issue. There has to be a national biobank. That is needed. There are other kinds of infrastructure issues here. This is just one part of this process that we are focusing on. So I'm not sure why we chose to focus only on this part.

DR. FITZGERALD: In part, in response to the public comments. I think also in part we thought this was reasonable in that response because when you talk about, obviously, the need for the biobanks and the repositories and large population studies and all that, some of that was already addressed in the Large Population Studies Report.

So the question, I guess, is, is this too granular? Which it may be as a recommendation and we don't need to put it in. But this was in response to the public comments, which we thought was a way of further specifying some of the things that had already begun to be addressed in the large population studies.

Go ahead, Suzanne.

MS. GOODWIN: Can you look at Recommendation 5B? Does this get closer to what you are talking about? 5B, 5D, 5A.

DR. RANDHAWA: It could come in there, also, because in 5B, as you are ending it, you talk about analytic validity, which is really getting into specimens and using them.

MS. ASPINALL: That would make me more comfortable, too, because I think this one, just as a recommendation that we are getting samples for the public but not enough connection to other things. So I think this raises anxiety from the public as opposed to reducing

anxiety.

DR. FITZGERALD: The reason this is in here is because, in the public comments, somebody said specifically this needs to be recommended. Now the question is whether or not we think it does. So if we don't think it needs to be recommended, we can just get rid of it because we have too many anyway.

I had Mike and then Jim and then Mara again.

DR. AMOS: If you are going to include this recommendation, I think it is critical that, really following on to Gurvaneet's statement, right now there are no standards for either obtaining, storage, or utilization of any biological specimens. There are no national standards for that.

So if you are going to include this recommendation, I would highly recommend that additional language be placed in the document to support the development of standardization for handling such specimens.

Now, if you are going to pull this out and put it in 5B, I will just jump ahead a little bit. If you are going to put it in 5B, maybe you should add NIST to the laundry list of people that everyone should work with.

But somewhere in this document, and it is a little anemic in this regard, you really need to emphasize the need for technology and sampling standards.

DR. FITZGERALD: Let me make sure I have it right. Jim and then Mara.

DR. EVANS: I was just going to really reiterate, I think, Kevin, when you were trying to point out why this was suggested. I think there is some valid rationale in having it, maybe with the modifications that Michael suggested.

The point being that clinical drug trials don't necessarily collect pertinent data and, really, the entire promise of pharmacogenomics rests on collecting certain samples, namely DNA, so that they are available for study when we begin to get response data, et cetera.

So I think it is a reasonable recommendation. I think something to the effect of what was just suggested about incorporating that into a usable, more comprehensive structure [should be included.]

DR. FITZGERALD: Mara.

MS. ASPINALL: I definitely agree that we have to provide some additional context. I think the question on No. 3 or No. 5, or maybe both, is this is the Clinical Research section and No. 5 is in the Establishing the Evidence Base section. My assumption, and again I'm looking at the public here, is that the idea is we wanted to mention it in the Clinical Research section because if it is not there it feels like it is missing.

I will try to spend a little time because I can't do this in real time, but I think we need to add some additional specificity on, as Michael suggested, what this means, how the samples would be used, or at least consistent with appropriate new national guidelines on this kind of work.

DR. FITZGERALD: "To enable the investigation of biomarkers associated with drug response within the development of national guidelines," or something along those lines? Just think about that. We have a few more comments to go to. Sarah.

MS. CARR: I just want to ask, I guess especially Mike, in terms of the standards and guidelines you are recommending, you are talking about technical issues rather than the ethical and legal issues? Because I'm sure you are aware of the NCI's guidelines. Those are

focused, obviously, on oncology samples.

But, are you suggesting, and others suggesting, that that is what is needed for this field? The way in which the samples are collected and stored, there needs to be standardization along technical lines?

DR. AMOS: Right.

MS. CARR: So it would be, in a sense, taking what NCI has done in oncology and focusing in on what is needed in this field?

DR. AMOS: Even NCI is in the process of putting more money into developing the standards for, for example, tissue because there are no real standards yet for how to collect and fix and store tissue samples for molecular pathology evaluation. So, yes.

DR. FITZGERALD: If we take a look at what is on the screen that Suzanne just put up, "To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical trials to request appropriate biological samples from research participants. HHS should develop guidance on how samples should be collected, stored, and shared."

Wait, wait, wait. I have Andrea. With the mic on, please. Thank you.

DR. FERREIRA-GONZALEZ: For our previous report in large population studies, did we ever recommend the development of these standards? Did we already do that?

DR. FITZGERALD: I have that on my computer, but I would have to dig that up. I'm trying to remember. Hunt is not here.

MS. CARR: Yvette, do you know? There is certainly a call for consideration of all the ethical issues. I think it was focused there, more on the ethical and legal and societal implications but not so much the technical, if I recall. But Yvette knows that report backwards and forwards.

DR. FITZGERALD: We will check with Yvette on that. Marc, go ahead.

DR. WILLIAMS: Just looking at the list of verbs at the end there, the one that seems to be missing is "used."

DR. AMOS: Yes, "utilization."

DR. FITZGERALD: Great. It was. It was one of the recommendations in the report. In the text, the body of this, we can obviously footnote that. That is a good point. We will make a mark, or someone will. That is a great idea. We have wanted to do that. We have wanted to integrate these reports. Exactly.

I have Gurvaneet and Michael. Still on this, right? We have to move on this, but go ahead.

DR. RANDHAWA: I think this is still incomplete because it is not just how well the samples are collected and stored, actually the issue is how well the clinical data are associated with the samples. Do we know if it is the same biological condition, the same disease, the same subtype. So that richness of clinical data is, I think, a major impediment, not just the technical issue of how well you collect and store it.

DR. FITZGERALD: But we have here how these "samples and their associated clinical data," if that is okay, "should be collected, stored, shared, and used." Good. All right.

DR. AMOS: Just one quick one. I was hoping that maybe you could change "request" to "obtain." Requesting is requesting. There is no --

DR. FITZGERALD: Well, you can encourage sponsors to obtain. You can do

that, right? Because that doesn't require their sponsors to obtain. You could require the sponsors to request. But you can't do both. So we can encourage the sponsors to obtain, or we can require sponsors to request. Take your pick.

Marc.

DR. WILLIAMS: No, I'm not going to use the "require" word, but I would like to suggest that the recommendation actually explicitly reflect the recommendation from the Population Study Report because a lot of times people don't read the whole report. So if we bury it in the text it won't be seen. That is consistent with what we have done in other reports where recommendations reference recommendations from other reports.

So whenever that is in there, I just say that should be inserted there in the recommendation, not just in the text.

DR. FITZGERALD: So you want the words from the other report put in here.

DR. WILLIAMS: Not the words but the specific reference.

DR. FITZGERALD: Oh, I see. A reference. Got it. So put like Footnote No. 1. Got it.

All right. We are still on this one. Julio.

DR. LICINO: I just have a comment. This is a little bit of a quagmire because --

DR. FITZGERALD: I think we have noticed that.

DR. LICINO: -- when you collect the samples it is very important to serve consent [so that] the patients know that the samples or the genetic data is going to go to the FDA or to regulatory agencies who are going to have access to that because the patient has the right to withdraw the consent and then to request that the data be changed. But once it is sent to the agency, I don't know that you can take the data away from an individual person. I don't think it is even possible to do that.

It really impacts a lot on the design of the studies, so I would maybe add a word here saying that future studies should be designed in a way that would permit deposition of data with the FDA if appropriate. If a study was not designed for that, you can have a sample but you cannot do it.

DR. FITZGERALD: Now, if we are developing guidance and standards on how these samples and their associated clinical data should be collected, wouldn't that be part of those guidelines and standards? Obviously it would involve informed consent, but it would also involve which ones are appropriate to that or not. Is that okay?

DR. LICINO: I guess so. I think it goes a little bit more than that. It is not the collection, it is the intent of the study.

DR. FITZGERALD: Right. But it would also involve "which should be collected," right? We need words here.

Who else had comments before? Mara, did you have something, too?

MS. ASPINALL: I just had a small one, which is sometimes we call it "drug response," sometimes we call it "drug metabolism," sometimes "drug prescribing," which I think they are meant to be the same.

DR. FITZGERALD: Oh, up there? Okay.

MS. ASPINALL: Not in this recommendation but comparing recommendations. Like, the last one we called it "drug prescribing" as opposed to "drug response." If folks think that those are interchangeable, I'm fine with it.

MS. GOODWIN: Which term is preferred?

MS. ASPINALL: I like "drug prescribing," which was broader than "drug response." That is how we did it on the last one, so it would suggest that we tried to be consistent with that.

I may be working off of the old version.

MS. GOODWIN: Do you know which previous recommendation?

MS. ASPINALL: 3C.

DR. FITZGERALD: "Drug development"?

MS. ASPINALL: Maybe it got out of 3C. It was there at one point.

DR. FITZGERALD: If everybody agrees "drug prescribing" is the preferred term, we can stick with that. No? Okay. That was a mistake.

DR. WILLIAMS: But I don't think we necessarily need to parse it. I think that the concept that Mara presented is a reasonable one, that we need to be consistent with our use of language.

DR. FITZGERALD: Yes.

DR. WILLIAMS: Rather than try and fix that here, which may be well impossible since we keep going back and forth, just a charge to the taskforce to say you need to be looking at "drug" and use the same language consistently unless there are specific reasons in a recommendation to make it different.

DR. FITZGERALD: Let me remind you, this is a finalization process. We don't have a chance further on from here.

DR. WILLIAMS: It's called lunch, Kevin.

[Laughter.]

MS. ASPINALL: Why don't we leave it as it is and then maybe as we look at the recommendations over lunch we can choose a word.

DR. WINN-DEEN: I just want to say, I think I agree with Mara because "prescribing" takes into account both response as well as ADRs.

MS. ASPINALL: That is what I was trying to get to.

DR. WINN-DEEN: Whereas if you just say "response," then you have left the other side of the whole PGx thing out.

DR. FITZGERALD: Steve.

DR. TEUTSCH: "Prescribing" gets you into the whole utilization and downstream consequences, and this is about clinical research, primarily, and really finding out what relates to the response, good and bad. I would leave it the way it was.

DR. FITZGERALD: All right. We are at loggerheads about whether to "respond" or "prescribe." Let's put it this way. If we started with "response," let's use that as our default. Are you okay with response in this recommendation? Is that okay, Emily? Or do you need "prescribing"? Since this is clinical translation.

MS. ASPINALL: How about we leave it as "response" now. I would like to, as we go back to it, just look to see if it needs to be consistent.

DR. FITZGERALD: Sure. Emily?

DR. WINN-DEEN: Yes. I think either we can leave it at "response" or "response/ADRs" or something.

DR. TEUTSCH: ADRs are responses.

DR. FITZGERALD: Right, right. Adverse drug response.

MS. ASPINALL: If you think it covers that, that's fine. I was trying to get the concept that it wasn't just initial drug response, that it was broader.

DR. FITZGERALD: All right. Everybody is good? All right. Let's go one more time through this.

"To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS should develop guidance and standards on how these samples and their associated clinical data should be collected, stored, shared, and used."

We could put in parentheses here or we could put a footnote, "Also see Recommendation," whichever number, "from the Large Population Studies Report." Okay? Okay. Great. Next. What? Not okay.

[Laughter.]

DR. FITZGERALD: This is why the NFL has that problem with that new rule. You can freezer the kicker at the last second.

DR. KHOURY: We want clinical data. What does that mean, Gurvaneet? We say this is drug use. Do you want other types of data, like risk factor data? When you are trying to link records and you are looking at outcomes, there are other data that are related to gene-environment interaction here.

DR. FITZGERALD: Wait a minute. Gurvaneet, did you have --

DR. KHOURY: What did you have in mind with "clinical data"?

DR. RANDHAWA: I was just trying to add on to the step that the initial recommendation as it was phrased was to focus on the biological sample collection and use. Now, depending on the context of how it is going to be used, it could be purely clinical or it could have more of a gene-environment, public health usage. So that I would leave up to the Committee as to how broad you want to make it.

DR. FITZGERALD: How about if we have now "associated patient data"? Is that better, worse?

DR. KHOURY: Not all participants are patients, however. They could be healthy individuals.

DR. FITZGERALD: "Participant data"?

DR. KHOURY: Because that keeps it vague. There is some clinical data but there is also drug use data and environmental, risk factor data, nutritional data, whatever.

DR. FITZGERALD: Marc and Paul the Questionable.

[Laughter.]

DR. WILLIAMS: This is in the context of developing guidance and standards. I think the point that Muin is bringing up is basically something that will be addressed in developing guidance and standards in terms of that. I don't think we need to parse it out anymore.

DR. FITZGERALD: Paul.

DR. BILLINGS: My comment is, there are two "shoulds" in the second paragraph. Maybe you should turn the second one into a "will."

DR. FITZGERALD: All right. Muin, developing the guidance and standards,

would that be part of what sort of data would be involved?

DR. KHOURY: Yes.

DR. FITZGERALD: "Other participant data will be collected, stored, and used." Where did you get the "should"? Oh, there. Got it.

All right. Now, try again. "To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS should develop guidance and standards on how these samples and other participant data will be collected, stored, shared, and used. Also see Recommendation whatever from the earlier Large Population Study."

"How samples and data" -- what is this? You have to push your button.

MS. CARR: How about --

DR. FITZGERALD: Wait a minute. We want to be happy with this.

MS. CARR: But I think it will help with that earlier discussion. "How these samples and the data associated with them will be collected." Then you have all the data associated with them. You don't define it one way or another.

DR. KHOURY: I like the word "participant" more than "data."

MS. CARR: The samples come from participants, don't they? We are not talking about anything but sample participants. Participant samples.

[Laughter.]

DR. FITZGERALD: Wait a minute. This is starting up again. Jim.

DR. EVANS: I agree with Muin. I think "participant data" is subtly but importantly different from just the accompanying data. That could be concentration of the sample.

DR. FITZGERALD: I hear people leaning toward "participant," where we have it now. Going once? No?

All right. So again, Sarah, what was your comment?

MS. CARR: How about "participant samples"?

PARTICIPANTS: No.

DR. EVANS: We are talking about the participants and other things --

MS. CARR: Their samples.

DR. EVANS: No, no, no. The sample is the chunk of tissue, the serum, the white cells, the DNA. What we are getting at here is --

MS. CARR: And all the associated --

DR. FITZGERALD: The crowd is turning uglier, Sarah. I would bail on this one if I were you.

[Laughter.]

DR. FITZGERALD: I don't know. I will throw Reed in front of you, but that is it. Beyond that, forget it.

I think we are good, right? Or, wait. No? Yes? No? Why? Who? Don't even ask, right. No, I think I have to ask.

All right. Next, 4A, page 35. Here we go. By the way, no one leaves until we are done, just so you know. If we are here at three in the morning. Isn't that how it works, Reed?

DR. TUCKSON: No question.

DR. FITZGERALD: "HHS should ensure that sufficient resources are available to FDA to build on and implement the agency's efforts to develop guidance on the codevelopment of pharmacogenomics drugs, and diagnostics. FDA's guidance should clarify the review process for codeveloped pharmacogenomics products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be. It also should promote collaboration between drug and diagnostics manufacturers."

Paul the Unimaginable.

DR. BILLINGS: Paul whatever I am. Again, can someone clarify why diagnostic manufacturers are specifically noted and why not, for instance, the laboratory industry, which is the major provider of these tests now?

DR. FITZGERALD: Emily.

DR. WINN-DEEN: The lab industry is right in the sentence before that.

DR. BILLINGS: Did I miss that somehow? Because of "laboratory-derived companion diagnostics," is that what you mean?

DR. WINN-DEEN: Right. I think what we were trying to ask FDA for was guidance on both aspects, those tests where they are just available through fee-for-service laboratories as well as tests that would be put in a box by an IBD manufacturer.

DR. BILLINGS: Right. But we want collaboration amongst all the entities in the provision of these things, don't we? In the last sentence it says, "Promote collaboration between drug and diagnostic manufacturers," but in fact we want collaboration across the whole spectrum of providers in this field.

DR. WINN-DEEN: Yes. So we get back into does FDA have purview over the labs. This recommendation was directed specifically at FDA to develop guidance.

DR. BILLINGS: I see.

DR. FITZGERALD: Mara and then Robinsue.

MS. ASPINALL: Can I make a suggestion that doesn't get to the issue whether FDA has purview, because I understand that is a bigger issue than even three in the morning. But I wonder if we just want to say "diagnostic companies" because that encompasses both manufacturers, lab service companies. It is broader, and the FDA has some draft guidance now and has ASRs that oversee things that the laboratory service companies do.

DR. FITZGERALD: Robinsue.

DR. FROHBOESE: I wanted to go back to the point that Muin raised earlier on when we were talking about the first recommendation, and that is use of the word "resources." This recommendation is calling for HHS to ensure sufficient resources are available. Recommendation No. 1 asked for NIH to put more resources into. Then we see Recommendation No. 5A, HHS should provide resources.

I think those are the only three that specifically talk about resources, and unless there is a particular reason why in this recommendation and other recommendations there is a need to emphasize resources, I would agree that we should just have an omnibus recommendation at the end, perhaps expanding when we get to it, Recommendation No. 15B, to talk globally about looking at needed resources to carry out the recommendations.

DR. FITZGERALD: In changing this one, how would you [phrase it]?

DR. FROHBOESE: I would just start with "FDA should" --

DR. FITZGERALD: "Build on and implement"?

DR. FROHBOESE: -- "build on and implement the agency's efforts."

DR. FITZGERALD: And then refer to 15B. Michael.

DR. AMOS: I'm just wondering if this recommendation covers when a drug company develops its own diagnostic. Is the language inclusive of that?

DR. FITZGERALD: That was trying to get back to your point, Mara.

MS. ASPINALL: No. My point was a different point. My point was the difference between diagnostic manufacturers and other kind of diagnostic companies. I actually think the way it is written now, "by diagnostic developers," does include that because it would say it doesn't matter what kind of company, it is a developer.

DR. FITZGERALD: All right. So we have "diagnostic developers." Good. What are we changing?

MS. GOODWIN: Sarah is asking that this be there.

DR. FITZGERALD: You have to talk into the mic.

MS. GOODWIN: Sorry. Should we say "PGx drugs and diagnostics" or "development of drugs and PGx diagnostics"?

DR. FITZGERALD: So, "drugs and PGx diagnostics."

DR. WILLIAMS: Codevelopment is the operative thing here. You are talking about a specific drug and a specific diagnostic that goes with that drug. It doesn't need any additional explanation.

DR. FITZGERALD: Marc, what are you saying? Should we go back to the way it was or do "PGx diagnostics" or just say "drugs and diagnostics"?

DR. WILLIAMS: No, I think the "PGx drugs and diagnostics" is just fine.

MS. ASPINALL: I would agree.

DR. FITZGERALD: Michael, go ahead.

DR. AMOS: By saying "codevelopment," doesn't that limit you because then, by definition, it has to be codeveloped with the drug. There will be other diagnostic tests that are pharmacogenomic.

DR. FITZGERALD: Those are addressed in other recommendations. This recommendation is specific to codevelopment.

All right. Let's read what we have now, I think. Wait a minute. Not yet. Emily.

DR. WINN-DEEN: I think the middle sentence, "FDA's guidance should," needs to take into account both processes where the diagnostic is developed by an IBD manufacturer and where the diagnostic is a laboratory-developed test. Somehow when we changed the last sentence, we lost the whole manufacturers part of the IBD industry.

DR. FITZGERALD: So, what would you recommend?

MS. ASPINALL: How about "and" instead of "but"?

DR. WINN-DEEN: Wait, wait, wait. I'm just trying to see where the right place to put this is.

DR. FITZGERALD: "Is subject to FDA review and the laboratory-developed companion diagnostic text may not be."

MS. ASPINALL: "And the laboratory-developed companion" --

DR. WINN-DEEN: The middle sentence is just one case where the drug is subject to FDA review but the diagnostic might not be. We need the companion sentence for when the drug and the diagnostic are subject to FDA review.

MS. ASPINALL: Could it be broader and just say, "The FDA's guidance should clarify the review process for codeveloped"? Do we need to clarify it all? Just say "codeveloped PGx products"?

DR. FITZGERALD: Andrea.

DR. FERREIRA-GONZALEZ: Take the "but the laboratory" out.

DR. FITZGERALD: Pardon?

DR. FERREIRA-GONZALEZ: Take "but the laboratory-developed companion."

DR. FITZGERALD: Wait a minute, wait a minute. Again. One more time. Take?

DR. FERREIRA-GONZALEZ: Take the part, "but the laboratory-developed companion," out.

DR. FITZGERALD: Stop the sentence after review."

DR. FERREIRA-GONZALEZ: Yes.

DR. FITZGERALD: Get rid of the rest of the sentence. There you go.

DR. FERREIRA-GONZALEZ: Some of these issues will be further dealt with in the next report.

DR. FITZGERALD: So, delete that part. We don't need the "including"? Get rid of "including." Start with "products." Okay. Try it again. We are into brevity, if we can do it.

All right. Let's see what we have. "FDA should develop and implement guidance on the codevelopment of pharmacogenomics drugs and diagnostics. FDA's guidance should clarify the review process for codeveloped pharmacogenomics products. It also should promote collaboration between drug and diagnostics developers." Muin, first to wade in.

DR. KHOURY: What do we mean by "should promote collaboration"? What does that mean?

DR. FITZGERALD: Beat them about the head and shoulders. That is how we do it here.

MS. ASPINALL: The text talks about some ideas where they could work together where they have pre-IDE meetings together. The Voluntary Genomics Submission data, in my mind, is one of those examples.

DR. FITZGERALD: We do have examples in the text. That is good enough? Okay. Anybody else? We need to move, and it looks like we are going to move. This looks good for the moment. Let's go to 4B. It is also on page 35.

"FDA's Office of Combination Products should coordinate the review of pharmacogenomics tests and drugs among the various FDA centers/offices to minimize delays in approvals of codeveloped pharmacogenomics products and to ensure timely access to such products."

[No response.]

DR. FITZGERALD: Great so far. Yes? All right. Excellent. Everybody is happy? No, Muin is not happy.

DR. KHOURY: Once you specify which part of FDA is needed to do the job, you can delete that third line, "among the various FDA centers and offices." It seems redundant to have that third line.

DR. FITZGERALD: Shorter is always better. "FDA's Office of Combination Products should coordinate the review of pharmacogenomics tests and drugs." Is this to go? "To

minimize delays in approvals of codeveloped pharmacogenomics products and to ensure timely access to such products." Yes? Yes. Excellent. Thank you. Wait.

[Laughter.]

DR. FROHBOESE: I think by taking out "among the various FDA centers/offices" the sentence may be too broad. So I would suggest the qualifier "should coordinate the FDA review." We are addressing only FDA, is that correct, as opposed to NIH review or CDC review?

DR. FITZGERALD: Yes, yes. Good.

MS. ASPINALL: Does that bring into account the fact that some tests are not reviewed by the FDA that wouldn't, by this, just become reviewed by the FDA? I was going to have a slightly different comment, but that may broaden it enough to get to that. Some of the PGx tasks are not under the FDA.

DR. FITZGERALD: But we are talking just FDA's review of PGx tests, right?

MS. ASPINALL: Well, I think with the addition it helps clarify that.

DR. FITZGERALD: All right. Going once, going twice, sold. On to the next. Great. No. 4C is on page 39 in your book, and there is a distinction between the way we have it on the screen and the way it is in your book. We will have to discuss that because there could well be a significant difference.

"HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products, especially for smaller," on the screen it says "markets." In your book it says "patient populations." "Markets" was our later rendition. Why markets? I think people wanted it to be broader than "patient populations."

DR. WINN-DEEN: So, are you saying we need to go beyond orphan drug kind of legislation and create a new thing that is based on markets instead of number of patients?

DR. FITZGERALD: I'm trying to recall why. I can't remember. We certainly can go with "patient populations." We are just putting in what was recommended. So if people want "patient populations," we can certainly do that. Is that okay, "patient populations"? Fine.

DR. WISE: I have a question on that.

DR. FITZGERALD: Sure. Please, Paul.

DR. WISE: Paul the Least.

[Laughter.]

DR. WISE: There are very large patient populations that represent very small markets. That should be captured in some way. What do I mean by that example?

DR. FITZGERALD: Yes.

DR. WISE: Development of drugs that would be extremely useful for millions of people around the world but are considered small markets. Incentives should be developed in accord with those considerations as well.

DR. FITZGERALD: I think in fact that may have been one of the points behind the "market" thing. Yes, Mara.

MS. ASPINALL: Maybe a question, but I think it gets to what Paul is getting to. You did in the summary the 200,000 patients or below for drugs. Where does the 4,000 come from? Is it related to the humanitarian drug exemption?

DR. FITZGERALD: Device.

MS. ASPINALL: Device exemption, sorry. But the HDE brings in a number of

other regulations around it. It has to go through IRB approval. It can't profit off of it. It seems to set up a very different standard, not only just the numbers. If the 4,000 is also subject to HDE, it seems to have a whole other hurdle of necessary regulations, approvals, and profit restrictions that the orphan drug piece does not. That was half a statement but really a question.

DR. FITZGERALD: Emily.

DR. WINN-DEEN: I think the point we were trying to make was to point that out. First of all, those two numbers are out of sync with one another. If you have a PGx system and it is orphan on the drug side, why is it not orphan on the diagnostic side. I think Steve Gutman provided the Committee with some insight that, really, the HDE is the only diagnostic mechanism that is available in an "orphan" kind of status. There isn't an equivalent to orphan drugs.

Correct me if I'm wrong, Steve.

DR. GUTMAN: No, that's right.

DR. FITZGERALD: Jim and then Mara.

DR. EVANS: I think that Paul the Wise's comment is a very important one and was, I think, the driving force behind changing it to "markets." Why not include both and say "for smaller patient populations and/or markets."

DR. FITZGERALD: That is, I think, what we are going to try and do, include both. Yes, Mara.

MS. ASPINALL: I think this gets to it in that way, the patient populations and markets, but do we get to a recommendation that goes to Emily's point about the differential here between the diagnostics and the drugs, or one that may not be effective?

DR. FITZGERALD: There is no recommendation that is specific for that, but we discussed that and whether or not there needed to be. The thought was, anyway, that what we were getting at was what we should recommend to the Secretary and not necessarily force something on that specific issue, though the understanding is that issue certainly would be addressed as part of the process of following up on these recommendations.

That left it open to how it might be resolved. We weren't going to recommend how to resolve it specifically.

MS. ASPINALL: I understand about how. I guess I'm recommending it should be more explicit, because I don't think you get it from this.

DR. FITZGERALD: Marc.

DR. WILLIAMS: The question that relates to the explicitness is whether it is under the Secretary's purview. In other words, is that able to be done under rulemaking or is this something that would require a legislative change to effect it. If it is the latter, we can't make an explicit recommendation about it. If it is the former, then we can.

DR. FITZGERALD: Sarah.

MS. CARR: I think you could recommend to the Secretary that he seek a legislative change, if it did require a statutory change. Does it, Steve? Is the 4,000 in statute?

DR. GUTMAN: I actually don't know.

DR. FITZGERALD: Mike. I'm sorry.

DR. AMOS: Just a logistical question. If I were looking at this recommendation if it were published in a list of recommendations, I think the way you are going to present this is you are going to have a separate sheet with a list of the recommendations along with part of an

executive summary?

DR. FITZGERALD: No. This will be part of the executive summary. This is part of the executive summary. There is not a special list just for the recommendations.

DR. AMOS: But, is there enough information in here that someone would know what you are talking about with this recommendation if it stood alone?

DR. FITZGERALD: If it stood alone.

DR. AMOS: Yes. If it stood on its own in a list, a separate list.

MS. ASPINALL: I would agree with Michael. I think in and of itself this is a piece of it. But I don't think it gets to, as Emily described it, the differential and the need to relook at, maybe at a minimum, the small patient/market issue around diagnostics. I don't think most people, if they are not in this room, would notice that.

DR. FITZGERALD: Granted there is always this tension between how much should go in the recommendation as far as exploratory materials and how much goes in the text. Now, there is more, obviously, in the report on all this, as we already saw.

Since it is a recommendation to the Secretary, as you say, if the public is seeking more information about what is explicitly involved in this, they can certainly look at the larger report. Even in the executive summary there are additional materials.

I guess the question is, if we want to wordsmith this to give it a little more content, how would you do it? What extra sentence or whatever would you want to put in? Suzanne is doing it right now. We need help, so if you have something. Michael? No. Marc?

DR. WILLIAMS: I have a suggestion. I think the issue that I have heard is it would be sort of a "whereas, therefore." "Given the inconsistency between the numbers of patients for orphan drugs versus the numbers of patients that would qualify for orphan devices and the inconsistencies between those two sets of rules, it is recommended that." That would at least give it some context.

DR. FITZGERALD: Wait a minute. Jim?

DR. EVANS: I don't know. I think that having the boxed recommendations brief and to the point makes a lot of sense. Then immediately under it you can say those kinds of things and put it in context.

I think brevity should be something we seek as long as it is clear and there is explanatory information accompanying it, even in the executive summary. They don't have to dig through it.

DR. FITZGERALD: Joe likes that, too. Wait. Steve?

DR. TEUTSCH: I think we have to be careful when we get into the sizes of these different things. It is very much the cost of development of these different things, drugs versus devices versus diagnostics, that lead you to needing different kinds of economic incentives. I think that is in here.

I agree with Jim that shorter is better.

DR. FITZGERALD: All right. Is this short enough? Let's take a look. Wait a minute. So, "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products. Specific incentives should be identified for smaller patient populations and/or markets to address inconsistencies between prevalence thresholds for orphan drugs and orphan devices."

No, too much. Kill the sentence. There we go. "And/or markets" we definitely

want. "For smaller patient populations and/or markets," right.

So we are back to, "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products, especially for smaller patient populations and/or markets," and making sure that that is explicated clearly in the materials.

Yes, Mara.

MS. ASPINALL: Maybe I have a simpler one. I guess the fundamental premise for me that I'm concerned about is, for orphan drugs, the system works as an incentive. For orphan devices or tests, the system currently works I think as a disincentive, with more restrictions than incentives.

Although I appreciate Jim's comment, I think we have context in a lot more of the other recommendations than this one. I don't think we are adding too much, but at a minimum to say the "development of PGx products and diagnostics," if you think about products as drugs or PGx drugs and diagnostics.

DR. FITZGERALD: Rather than "products."

MS. ASPINALL: Yes, so it is clear. Because some people will consider products being drugs. Not everyone. But I wanted to highlight "diagnostics" because I think the HDE process today works as a disincentive.

DR. FITZGERALD: Right. Paul.

DR. WISE: Thank you. There are really two concerns here. One is this technical conversation about different types of pharmacogenomic developments. But there is a great sensitivity that I think generated in part the conversation around this recommendation coming into this meeting and that is outside of the issue. There is great sensitivity about small patient populations and very large populations that are small markets. In other words, large populations of people who can't pay.

If it was going to require greater technical precision to address the points that you are making, it is also going to have to be balanced by a strong statement that also elevates this issue of small patient populations and markets. So if you are going to put in extra language to clarify that, it might require moving to a 4D that explicitly elevates or addresses the sensitivity around small patient populations and small markets.

DR. FITZGERALD: Look at what we have now. Is that sufficient emphasis?

DR. WISE: If more language was going to be placed to clarify the issues that you are raising, my concern was that --

DR. FITZGERALD: It would be lost. Right. Got it. George, look at what we have now. "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics drugs and diagnostics," rather than "products," "especially for smaller patient populations and/or markets." Does that get to where we want to go? Yes, yes, yes? Yes. Excellent. Very good. Next.

We are supposed to break at noon, so if we can get one or two more done, that would be dynamite.

Page 43 is where you will find Draft Recommendation 5A. "HHS should provide resources to identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics. Progress will require high quality data resources, improved methodologies in the design, conduct, and analysis of observational studies,

and empirical research on the evidence and standards necessary for making decisions for various purposes (for example, coverage, clinical guidelines, performance metrics) in different clinical contexts."

This is getting at establishing an evidence base. Everybody seems happy. No? Paul.

DR. BILLINGS: This is, again, a background question. The report is surprisingly devoid of the evidence of current use of testing. In other words, there isn't a table that shows what the frequency of use of TMPT or P450 testing or whatever. So we are advocating for the establishment of the database, yet there doesn't seem to be any review of the data in the report. So I'm curious about why that occurs.

DR. FITZGERALD: Mostly because the data is not there.

DR. BILLINGS: What does that mean? The people who are providing the tests are not keeping data; is that what you are trying to tell me?

DR. FITZGERALD: Marc, go ahead.

DR. WILLIAMS: Yes, there are a number of different issues. First of all, any sort of an outside agency that wants to review that, because of the coding deficiencies, can't collect the information. You can't tell based on genetic CPT codes whether this was a TMPT test or an invader assay or a BRCA or whatever.

So the third-party payers that may want to look at utilization can't develop data or ask how many of these tests are being done. Manufacturers are variable in terms of their willingness to put their data out for public review in terms of numbers, results, et cetera. So there are no sources of data in the available public literature that can give any sort of an estimate about utilization on this.

DR. BILLINGS: Can I just follow that up? Does that mean that the Committee or somebody asked the providers of tests in this sector to voluntarily provide the data and they refused?

DR. FITZGERALD: No, we didn't do that. Steve, go ahead.

DR. TEUTSCH: This is actually an issue that is addressed in the Oversight Report. We talk about much more the translational process into clinical decision support. There is a section in there, and I think it is worthwhile making sure that we cross-reference appropriately in anticipation.

DR. BILLINGS: The Oversight Report is going to come out much later than this, presumably.

DR. TEUTSCH: No, I understand.

DR. FITZGERALD: Steve, actually, we can't. My understanding, from what has been implanted my brain by Sarah, is we cannot anticipate because nothing has been voted on yet for that report. But I think that report could then certainly reference back to this one. You can do that.

But no, we didn't attempt to do that because our idea was to look at what the terrain is currently. The terrain currently was that that information wasn't available.

DR. BILLINGS: I'm aware of the lack or the unevenness of the published data, but that doesn't mean that there aren't ways of voluntarily providing at least some of the parameters of this data. Some of these tests have been in the public domain for a long, long time.

DR. FITZGERALD: Was there something you wanted to then address in the recommendation?

DR. BILLINGS: I think it is a striking deficiency of this report that there is no compilation, or at least some comment about the compilation, of data in this area.

DR. TUCKSON: We will make sure we go back into the narrative of the report and reference the fact that there is stuff going on. The key word in this recommendation is the word "progress." Maybe we can deal with it that way. Let's beef up the narrative a little bit.

DR. FITZGERALD: Jim. No, okay. Barbara.

DR. McGRATH: I wonder if it would make it simpler just to remove some of the methodology part, the words from "progress will require." Just state something like "Using acceptable methodologies" or something in the top and then explain in the report what methods you are suggesting. Aren't those standard methods for clinical validity, utility, and cost effectiveness?

DR. FITZGERALD: We did have a discussion on that, and some people thought it was important to have that detail, but we can still have that discussion.

Who is going? Steve.

DR. TEUTSCH: I can go either way. The point is that the methods aren't developed and they are not accepted generally in the use of observational and some of these other things. Now, whether you want to include them here is another question, but there is a general problem in a lot of the evidence-based medicine approaches. It is not unique to this. How to incorporate them in an accepted manner is still a subject of considerable debate.

DR. TUCKSON: Let me just ask Barry and CMS, on this word in the recommendations: "In empirical research on the evidence and standards necessary for making decisions for various purposes, whether it is coverage, clinical guidelines, performance metrics," from your point of view, is [it] research on the evidence and standards, or research that supplies the evidence? I mean, we know what the evidence and standards are, don't we?

I'm wondering, are you trying to suggest we should try to do more research on what evidence and standards are necessary to make decisions, or research that answers the evidence basis of making these decisions?

I think the people that are making clinical coverage decisions and guidelines decisions pretty much know what those guidelines are. They don't need any more research on the guidelines; they need the answers.

DR. STRAUBE: I think it is primarily for coverage purposes, Reed; the latter. So I would agree with you.

I was going to suggest that in fact in the parentheses there we put "coverage, clinical guidance, performance metrics." Something that will sit well with the Secretary, believe me, since he usually talks about this would be value-driven health care, putting that in there, too. It goes beyond those three categories. It gets into improving quality, improving efficiency, et cetera.

DR. FITZGERALD: So, to add "value-driven health care" after "performance metrics."

DR. STRAUBE: Correct.

DR. FITZGERALD: "Value-driven health care." Did I miss someone over here? Marc, go ahead.

DR. WILLIAMS: Just to respond to Reed, I think the issue for me relating to your specific question is that the key issue in the first sentence is "identify evidence gaps." I think we don't necessarily know what those evidence gaps are. Some of them may be related to quality of evidence. Some of them may be related to actual clinical data. So I think it captures the points that you made.

DR. TUCKSON: The reason why I was asking, and you hit it exactly, was it sounded like there were two moving variables in the equation and I wanted to lock one in. It is the evidence gap that is necessary to answer the paradigm of decision-making as it exists in the real world today. I didn't want to figure out what the paradigm of decision-making research is and then figure out what the gaps are at the same time. You are trying to hit two moving targets.

Basically, let's move it along, folks. We know what it takes to answer these questions. We know how people think about it every day. Now let's provide the data and the information necessary to answer the questions.

DR. FITZGERALD: Did you want to recommend a change in the wording?

DR. TUCKSON: Yes. "Research that supplies the evidence" instead of "research on the evidence."

DR. BILLINGS: It has been my experience that the evidentiary requirements differ amongst different agencies, private, public, so forth and so on. Unless, Reed, you are going to allow for some harmonization, again, of what the evidence standards are and have them have some bite across the public and private sector, I don't know quite exactly how you are going to resolve that.

DR. FITZGERALD: Jim.

DR. EVANS: I would advocate leaving it the way it is, Reed, because I don't think it is a no-brainer as to what evidence really is important and what should drive change, acceptance, et cetera.

Muin works on this stuff. I think he might want to weigh in, or he might want to run out of the room.

[Laughter.]

DR. EVANS: I would advocate leaving it the way it is.

DR. TUCKSON: Can we say both? Can we say "research on the evidence and standards necessary" -- all right. That's fine. If you want to leave it there, that's good. I don't want to prolong it. I will withdraw the suggestion.

DR. FITZGERALD: That is a marvelous template by the Chair to lead us forward into the afternoon, to be very open. Yes, go ahead, Mike.

DR. AMOS: If you are talking about analytical validity and you are talking about standards, I want to bring up the point that there are only a handful of actual physical standards for diagnostic tests available. If part of your evidence gap is the reliability of the assays, then you really should put some additional language in here regarding the actual physical standards and standardizing the technology and the platforms.

DR. FITZGERALD: So what would you recommend?

DR. AMOS: I will have to think about it.

DR. FITZGERALD: No, you have to have answers. Hold on, hold on. Andrea, go ahead.

DR. FERREIRA-GONZALEZ: I think we will deal with that in the next report,

even though we can't talk about the next report, the Oversight.

DR. FITZGERALD: Right, right. Sarah, can we say in this report that another report is underway that is going to attempt to address it, or something like that? So we can footnote? Okay. We will make sure that is in the text, that that question is being addressed more completely in a subsequent report. That we can say. I don't think we can say exactly what we are going to say.

Robinsue.

DR. FROHBOESE: A very quick edit for consistency. Should we take out "should provide resources" and it should read instead "HHS should identify and address evidence gaps"?

DR. FITZGERALD: Are people comfortable? Okay. Great. Thank you. "HHS should identify"; do you have that? Great. Ready? Here we go.

"HHS should identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics. Progress will require high quality data resources, improved methodologies in the design, conduct, and analysis of observational studies, and empirical research on the evidence and standards necessary for making decisions for various purposes (e.g. coverage, clinical guidelines, performance metrics, value-driven health care) in different clinical contexts."

We have been told we are done.

DR. TUCKSON: We are done. Now let's do a quick process check here. If we think about this, we have now from when come back at 12:45 until 4:30 to go through all the rest. So I think we are about okay. I'm a little nervous, but we will push through.

What did you say?

DR. TELFAIR: I haven't said anything yet. I was getting your attention.

DR. TUCKSON: You got it.

[Laughter.]

DR. TELFAIR: Just maybe a point of order. In other work that we have done in other groups, we have set a time limit on progress related to certain activities, given how you break it up. I realize that there may be a need for process on some of these things, but I think that if we set a time limit that will accelerate our thinking and really make us come to a decision much quicker.

So if the plan is to try to get through a large set of recommendations before the end of the day, I would recommend, and that is a group decision, that we set some kind of time limit on the amount of dialogue we have, either by recommendation or by block of recommendations or some parameter of time that allows us to really be focused.

DR. TUCKSON: Thank you for that. We are going to do the quantum calculus in just a second and, during lunch, figure out where we are, how many recommendations we have left. That is great, Joe. I think we will do that. But one way or another we will get through it.

[Lunch recess taken at 12:03 p.m.]

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

[Reconvened 12:48 p.m.]

DR. TUCKSON: Welcome back. Apparently we have some considerations on 4B

DR. FITZGERALD: We took care of it.

DR. TUCKSON: On 4B? We don't now? We took care of it?

DR. FITZGERALD: We took care of it.

DR. TUCKSON: You took care of it offline?

DR. FITZGERALD: Yes.

DR. TUCKSON: Wow. Some kind of controversy that turned out to be.

DR. FITZGERALD: I threatened them. It worked out real well.

DR. TUCKSON: Can you all believe this? This is perfect. Everyone came back exactly on time. They knew we were going to start.

It has come to my attention, from mean people like Marc, that apparently I once again, instead of calling him "Gurvaneet," I called him "Gurvanot," and everyone has been snickering about it the whole time.

For the new people that don't know, I mangle everyone's name regularly. That is my responsibility. But of all the people that I mangle every time, it is Gurvaneet Randhawa.

[Applause.]

DR. TUCKSON: Which really takes all the fun out of it when you screw it up.

[Laughter.]

DR. TUCKSON: So I will find someone else's name to butcher horribly before my tenure here is over. Unfortunately, Gurvaneet is off the table now. We have this new Paul the Wiser, Paul the Something, and Paul the Lesser, which is incredible.

Take it away, sir.

DR. FITZGERALD: Thank you, "Red."

[Laughter.]

DR. TUCKSON: We are on 5B. So, gearing up again after lunch. Get those synapses firing. You will find 5B on page 43 of your report, Tab 3. It reads, "HHS should initiate and facilitate collaborations between public," for example that long list of acronyms, "and private entities (for example, private health insurance plans, pharmacy benefit managers, healthcare facilities with electronic medical records, clinical research databases, or genetic repositories) to advance the generation and sharing of knowledge on the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics."

Yes, Michael.

DR. AMOS: Can you just add NIST there to the list?

DR. FITZGERALD: Sure. Oh, it is already up there. Sorry.

Oh, I love this. This is good. Oh no, wait. Go ahead.

DR. EVANS: A real simple thing. Again, it gets back to what I was saying on the prior one. I noticed it in the first sentence of 5A, too. It is very research-focused but [we need] the term "value." There is cost effectiveness in there, but if you insert "value" into the first sentence of 5A and also in 5B, it gets at quality and cost.

DR. FITZGERALD: Is that not under clinical utility?

DR. EVANS: Not really.

DR. FITZGERALD: So we need just "value"?

DR. EVANS: I would add it because cost effectiveness is way too narrow. I think we are looking for a bigger picture here.

DR. FITZGERALD: Let me get this right. So it is "analytic validity, clinical utility, cost effectiveness, and value"? Just the word "value"?

DR. EVANS: Right.

DR. FITZGERALD: Everybody comfortable with that?

DR. EVANS: The same phrase is present in 5A, so you may want to change that to be consistent.

DR. FITZGERALD: Great. Excellent. We have made just a couple of changes. "HHS should initiate and facilitate collaborations between public," including NIST, "and private entities," including that whole list, "to advance the generation and sharing of knowledge on the analytic validity, clinical validity, clinical utility, cost effectiveness, and value of pharmacogenomics."

Good? We are good to go. Fantastic. Next is 5C. Same page in your report.

"HHS should encourage and facilitate studies on the clinical validity and clinical utility of pharmacogenomics," and we will see about value, "and the dissemination of study findings, including negative findings where appropriate, through publications, meetings, and an information clearinghouse."

Yes, Marc.

DR. WILLIAMS: Do we need "where appropriate"?

DR. FITZGERALD: The question here was since, obviously, you are going to get lots of negative findings, some which may or may not be relevant, would "relevant" be better? I suppose it doesn't do any more specificity than "appropriate." Just say "including negative findings."

DR. WILLIAMS: Right. There is a reasonable amount of literature that says that this is a major issue.

DR. FITZGERALD: No, it is.

DR. WILLIAMS: So I think just saying "and negative findings" is sufficient.

DR. FITZGERALD: It is not too draconian for anyone? Fine. Get rid of it. Good.

All right. Anything else on this?

[No response.]

DR. FITZGERALD: Great. So everybody is good. "HHS should encourage and facilitate studies on the clinical validity and clinical utility of pharmacogenomics and the dissemination of study findings, including negative findings, through publications, meetings, and an information clearinghouse."

We are good on that? Everybody looks happy. Excellent. Next. Fantastic. Thank you.

"NIH should provide mechanisms that promote interactions among basic, translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions would be to maximize the value and utility of basic and translational research data for downstream assessments of the clinical validity and clinical utility of pharmacogenomics tests."

You will notice this ends here. What is in your report has another sentence. We are recommending deleting that sentence and just stopping here. Yes.

DR. WILLIAMS: Should it read "NIH" or should it read "HHS," since there are other HHS agencies involved in that kind of work?

DR. FITZGERALD: "HHS." Good. Thank you. Anyone else? This is good. We should have lunch more often.

[Laughter.]

DR. FITZGERALD: Going once, twice, three times. Fantastic. Sold. Next.

No. 6A is on page 47 of your report. Again, this is slightly different on the slide than it is in your text.

"HHS should encourage private sector entities, including academic institutions," and here is where the difference is, "voluntarily to share," we are doing a little wordsmithing ahead of time, "voluntarily to share proprietary data to advance the development and codevelopment of pharmacogenomics products. Manufacturers should be encouraged to make their data publicly available to allow others to conduct research and publish such studies."

We decided not to split the infinitive and not make English professors across the nation unhappy with us.

DR. FOX: I think "voluntarily" may be in the wrong place there. It sounds like you are voluntarily encouraging. You might want to put it after.

DR. FITZGERALD: "To share voluntarily"? No, because that splits the infinitive.

DR. FOX: "Share proprietary data voluntarily."

DR. FITZGERALD: "To share proprietary data voluntarily." Okay.

Anything else with this, now that we have finally decided where we are going to volunteer? Trust me, we had long discussions about this.

So the final is, "HHS should encourage private sector entities, including academic institutions, to share proprietary data voluntarily to advance the development and codevelopment of pharmacogenomics products. Manufacturers should be encouraged to make their data publicly available to allow others to conduct research and publish such studies."

Fantastic. All right. Moving right along. This will make "Red" very happy. No. 6B. Gurvaneet, by the way, is giving me $10 every time I say that. I just want you to know.

[Laughter.]

DR. FITZGERALD: No. 6B. "HHS should work with the private sector to identify obstacles to data sharing and to develop solutions to overcome these obstacles. For example, legal and data confidentiality assurances, intellectual property protections)."

Ruminations, suggestions? Yes.

DR. EVANS: We have been working on this extensively over the last year or two in terms of Medicare data, claims data in particular. One thing I would suggest you put in the parentheses is "funding."

DR. FITZGERALD: Funding.

DR. EVANS: You have focused in on legal issues and what not, but who will pay to collect data and share it.

DR. FITZGERALD: Oh, funding of the data collection.

DR. EVANS: Yes.

DR. FITZGERALD: So, "funding of data collection" rather than just funding? Right? Specifically data collection.

Anyone else? Marc.

DR. WILLIAMS: Just a purview question. Barry, maybe you can comment on this. The intellectual property protections, would that be within the purview of HHS or does it have to work with another agency within the federal government to deal with that? I don't know.

DR. STRAUBE: No, that can be within HHS. There are other agencies that might need to be pulled in, but definitely it could be HHS.

DR. FITZGERALD: Paul the Middle.

MR. MILLER: I'm not sure, but are confidentiality and privacy the same thing?

DR. FITZGERALD: No, no. I don't know about legally, but ethically, no.

MR. MILLER: So, do you want to also add something in here about privacy assurances in addition to confidentiality assurances, or is that something different?

DR. FITZGERALD: I think that is different, but I'm willing to be corrected.

MR. MILLER: Is it different?

DR. FERREIRA-GONZALEZ: At least my understanding of it.

MS. ASPINALL: This is for the company as opposed to privacy for the individual.

DR. TUCKSON: Are there any HIT issues here, and does that need to be put into the parentheses section?

DR. WILLIAMS: The good news is this is not an exclusive or a restrictive list. Other things could be added as HHS feels necessary.

DR. FITZGERALD: We do try to deal with the HIT issues later, but we could certainly put that in here, too.

MS. ASPINALL: I think it is a good idea, given the Secretary's focus on HIT, around personalized medicine. I think it is great to add it as an example.

DR. FITZGERALD: We could do "funding of databases and health information technology." Thank you, Suzanne.

So we have, "HHS should work with the private sector to identify obstacles to data sharing and to develop solutions to overcome these obstacles. This list includes but is not exclusive, legal and data confidentiality assurances, intellectual property protections, funding of databases and health information technology."

Everybody is happy? Great. Thanks very much. Next is 6C. This is found on page 48 of your report. Now we are into the data sharing and database interoperability.

"Research, regulatory, medical record and claims databases need to be interoperable to facilitate research on pharmacogenomics technologies and to build the necessary evidence base. Interoperability of these databases will facilitate the study of the molecular pathogenesis of disease, the identification of targets for drug development, validation of pharmacogenomics technologies, assessment of health outcomes associated with the use of pharmacogenomics technologies, and determination of the cost effectiveness and economic impact of using these technologies.

"HHS and other relevant departments (for example, DVA and DOD) should work with the private sector to improve data sharing and interoperability among database. Specifically, HHS should work with existing organizations to create uniform genomic data

standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange."

Yes, Ellen.

DR. FOX: A couple of points on this. First, I think the first sentence is overstated. I think interoperability is nice to facilitate those things, but I don't think you need interoperable records in order to conduct research. So I think that "need to" is a little bit overstated.

DR. FITZGERALD: I think the "need" is to facilitate.

DR. FOX: They need to be interoperable to facilitate.

DR. FITZGERALD: Right. To facilitate research.

DR. FOX: No, I'm saying it is not really a need. It is helpful.

DR. FITZGERALD: You could facilitate it other ways.

DR. FOX: Yes, yes. The second point, I think there is technically a difference between data sharing and interoperability. In the second paragraph it talks about data sharing and interoperability. So perhaps that should also be in the first sentence.

DR. FITZGERALD: Oh, I see.

DR. FOX: I'm suggesting maybe combining the first two sentences and saying "Data sharing and interoperability of various databases, e.g." and then put the list in the first sentence, "will facilitate."

DR. FITZGERALD: Let's just make sure we got what you are recommending.

DR. FOX: That is what I'm recommending. Then, a second point. This isn't on the recommendation but in the text. I think the text lists a number of barriers to interoperability which are basically logistical or practical barriers. I think it is important to note that there may also be some philosophical barriers to interoperability.

In other words, you might read this to suggest that ideally every database should be interoperable with every other database. I don't think that is accurate. I think that there may be, for example, differences in the way the data was collected, the purposes for which it was collected, the mission of the organizations, where just combining databases would not be appropriate.

DR. FITZGERALD: This is a perfect time to once again remind everybody to do this. Anybody who has any recommendations for the text itself, please get those recommendations, very specific [as to] where you want it in the text and what you want in the text to Suzanne. That can be done today or you can Email her shortly after this meeting. But whatever recommendations you have along those lines, please get them to Suzanne and we will incorporate those into the text. So, thank you on that note.

Yes, Gurvaneet.

DR. RANDHAWA: There were two issues for me. One, the first paragraph starts out very broadly in looking at claims databases, medical record databases, and then the second paragraph ends very narrowly in just genomic database standards. Is there a reason to exclude the others from that?

DR. FITZGERALD: If I remember correctly, the idea was that yes, while we did want the more generic to be in the recommendation, there was discussion where people wanted to make sure that specifically that narrow area of creating uniform genomic data standards and exploring ways to harmonize was mentioned.

So this is one of those where we thought just the generic recommendation wouldn't be sufficient but that needed to be mentioned. That is the reason, if I remember correctly about how that came about.

MS. GOODWIN: You say the second paragraph is specifically focused on genomics. Oh, just on genomic data standards.

DR. RANDHAWA: Right. Which is not how you start out.

DR. FITZGERALD: Right. We started with the generic and the broad, but the people in the taskforce thought it was important to make sure that that was specifically mentioned. That is all I can tell you.

DR. RANDHAWA: Then the second issue was, some people are distinguishing data sharing from information sharing. Data sharing implies access to the data that is present in a database, which may or may not be feasible [because of] intellectual property issues or privacy issues but also business model issues.

Some folks have suggested that it may be feasible to share information that is present in the databases without actually sharing the data per se in the databases. I don't know if you want to make that distinction here.

DR. FITZGERALD: That is a good question. Again, my recollection of our discussion of this particular one was on the data and not the information because, obviously, if there is information sharing, there has already been a process of filtering and interpretation that has been ongoing. That doesn't necessarily give the person access to the data. The raw data, if we want to put it that way, not that there is such a thing. But the data itself rather than how the data has already been processed.

Again, we can discuss that. But that I think, if I remember correctly, was the point.

Yes, Paul.

MR. MILLER: Just a drafting issue. I'm agnostic on the point, but it strikes me that this recommendation is drafted very differently from the others. All of the others are really much more directive and start off "HHS should," "NIH should." This has an introductory paragraph which really isn't a recommendation for action but rather a broad statement and then the recommendation comes differently.

So my question is, assuming this is done purposefully, does that make sense just in terms of creating the recommendation or is that better served being put in the text?

Because it really stands out as different in terms of format from the rest of the recommendations. If you look at the other recommendations, they are all "HHS should," HHS this, that, and the other thing. Here we have just an open paragraph of a statement.

DR. FITZGERALD: Again, this gets back to that tension that we felt before when we were talking earlier about the need to put in a little justification into the recommendations. Granted this is for the Committee to decide.

MR. MILLER: As I said, I'm about agnostic about it being there. I just want to point out that it is very different from every other recommendation.

DR. FITZGERALD: Right. I think the idea was that this was useful here, but in any case. Marc.

DR. WILLIAMS: I would just offer the suggestion that if you flip those two paragraphs then it would fit the format that the other ones have.

MS. ASPINALL: I'm quite taken by Paul's comment as to whether we need the now-second paragraph. I think it is otherwise in the executive summary in the same way the others have the assumptions.

DR. FITZGERALD: Yes. If we want to whittle this down, we certainly can.

DR. WILLIAMS: I would just note that several of the other recommendations that we passed through, 5A in particular, do in fact include a small amount of text that put them in context. I don't see any reason not to do that.

DR. FITZGERALD: Yes, sure. Scott.

LT. COL. McLEAN: There are a few locations where the Department of Defense is named specifically, and this is one of them. In this context, it seems to imply that we are going to recommend that the Department of Defense work with the private sector. Is that a recommendation for the Department of Defense specifically?

DR. FITZGERALD: The idea, I think, in this regard was [for] Department of Defense and Department of Veteran Administration.

LT. COL. McLEAN: Usually this is a recommendation for the Secretary to take some action.

DR. FITZGERALD: For HHS, right.

LT. COL. McLEAN: The way this is worded, it suggests that it is a recommendation to the Department of Defense. I just want to clarify that.

DR. FITZGERALD: Got it. Right. No, no, no, this is a recommendation to the Secretary. Maybe you are right; we could word this better. The idea, anyway, was to collaborate with the other departments in moving to the private sector.

DR. WILLIAMS: A language suggestion there would be to remove the "and" and just put "work with other" or "convene," which we have used in other recommendations. We cannot make specific recommendations to other departments.

DR. FITZGERALD: Right. It is not recommending to DOD, correct. Or DVA, for that matter.

DR. AMOS: If you are going to make that change, actually NIST has a role in interoperability and data standards. So you can just add NIST to the list.

DR. FITZGERALD: As part of the e.g. list?

DR. AMOS: Right.

DR. FITZGERALD: Let's see what we have at the moment. Now we have reversed the paragraphs. So we have, "HHS should work with other relevant departments (for example, DVA, DOD, and NIST) and the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange."

Second paragraph. "Data sharing and interoperability of research regulatory medical record and claims databases will facilitate the study of the molecular pathogenesis of disease, the identification of targets for drug development, validation of pharmacogenomics technologies, assessment of health outcomes associated with the use of pharmacogenomics technologies, and determination of the cost effectiveness and economic impact of using these technologies."

That is where we are at the moment. People are good with that? Any other

questions, comments, or general malaise?

[No response.]

DR. FITZGERALD: Good. All right. Excellent. Next. On page 49 of your report, Draft Recommendation 6D, "FDA should identify, initiate, and facilitate research opportunities and public-private partnerships to encourage the development and codevelopment of pharmacogenomic products (for example, through the Critical Path Initiative.)"

Yes, Chira.

MS. CHEN: This sounds like FDA is paying for the research. So, it is?

DR. FITZGERALD: "Should identify, initiate, and facilitate research." I wouldn't say paying for all of it.

DR. GUTMAN: The deal for the Critical Path is it is very largely being generated out of leveraged activity, so collaborative activity. Funding has been modest up until now, and there has been a deliberate effort to make sure that that funding is always matched in some way.

I think the funding may become more generous. We are never going to look anything like even a small nook or corner of NIH, so I'm certain that it would continue to look for partnerships with industry or other government entities.

MS. CHEN: I just want to make sure that is being done, or else why are we putting it on here.

DR. FITZGERALD: Anyone? Yes, Michael.

DR. AMOS: The NIH has their Biomarker Consortium. Is that mentioned anywhere? It could fit here as well. That is a public-private partnership that would be along the same lines as the Critical Path.

DR. FITZGERALD: Now, there is an appendix in the report, just to let everyone know, of all the various efforts that are going on in the government. Is that Appendix A?

MS. GOODWIN: Yes. There is discussion in the text of the report about the Biomarkers Consortium, and it is also in the appendix. That is part of the reason why the "e.g." is here noting that this is just one example of one of the activities that it could be done through. But, if we want to add others or not mention any specifically.

DR. FITZGERALD: If anybody notices in the report an effort or a program is missing, please, again, let Suzanne know and we will be happy to add things to the list. We want to be as comprehensive as possible. Marc.

DR. WILLIAMS: I think the thing that looks a little bit different here is we have identified just one, whereas in many of the other recommendations we have identified more than one. It may, appropriately or not, give pride of place, if you will. If we want to have a e.g., it might be good to mention a couple.

DR. FITZGERALD: So we will do "Critical Path Initiative or Biomarkers Consortium."

We haven't made too many changes to this, so it stands almost as read initially. Everybody is good with that?

[No response.]

DR. FITZGERALD: Fantastic. It looks great. All right. On to the next. No. 7. This is on page 51 of your report. This is into, now, the realm of personal information protection.

"As data access and sharing expand, it will be important to strike the right balance between protecting the privacy and confidentiality of personal data and fostering access to these data for pharmacogenomics research. Stronger data security measures may be needed as more pharmacogenomics researchers access patient data."

"It will be important to strike the right balance." Well, okay. "HHS should strike the right balance." "Should work to strike" or "guide" or whatever. Yes, Paul.

DR. BILLINGS: I have a problem with this particular recommendation because it is important now, it is important in the future, and it was important in the past as well. So, what is exactly new about this? What are we calling for that isn't already in place?

DR. FITZGERALD: I think the reason behind it was exactly what you just said: its importance. So the thought was to leave it out, its absence might suggest that it is not as important as it is. It is not to say that this is the definitive recommendation or that this changes anything from the past or reduces anything for the future but to say it is of such importance that it needed to be in here. But I think that was part of the idea, that it is in fact such an important issue.

Marc, go ahead.

DR. WILLIAMS: To address that and to expand a bit on the recommendation, I think that the issue that has resurfaced that does make it a bit different is the idea of the information technology and whether or not previous recommendations have in fact been specific enough to capture that.

What I would reference is the work that is being done through the American Health Information Community, AHIC, which is a DHHS initiative that has a specific workgroup on privacy. I think this would be a perfect opportunity to make a very specific recommendation and say that we recommend that the Secretary raise this specific issue with the Privacy Workgroup of AHIC to develop guidance as part of that initiative.

DR. FITZGERALD: Joseph.

DR. TELFAIR: I don't have anything to add to the last comment, but I thought the recommendation should start off with a much stronger statement. So the last sentence, I would actually recommend it be the starting sentence, and I would change the word "may" to "will." Whatever comes after that the Committee can decide, but I would just move that around.

DR. FITZGERALD: Done. Then I have Mara and then Barry and then Robinsue.

MS. ASPINALL: The same comment.

DR. FITZGERALD: Oh, okay. That's good.

DR. EVANS: Just in addition, Marc, to the Privacy Workgroup, there is the Personalized Medicine Workgroup.

DR. WILLIAMS: It is a different workgroup under the AHIC. But what the Personalized Health Workgroup has agreed to do is to work with the Privacy Workgroup on these issues. So it would really be captured within that discussion.

DR. EVANS: That works fine. I think what some of us within HHS are trying to do is to cut down on the number of workgroups that are there.

[Laughter.]

DR. EVANS: Thank you.

DR. FITZGERALD: Robinsue and then Paul.

DR. FROHBOESE: In response to this discussion, I just wanted to point out Draft Recommendation No. 12A, which specifically does reference AHIC. That may be the place to get some greater specificity, although it is fairly specific. Underscore the privacy and security in that recommendation.

DR. WILLIAMS: I would just note that that one has a little bit of a different orientation in the sense that it is really looking at decision support, which is a different aspect of that. We have several recommendations here around Nos. 6 and 7 that are relating to the database, so I don't know that we necessarily need to combine them, although if everybody feels strongly about that I think that would be fine, too.

DR. FITZGERALD: Paul.

MR. MILLER: As a matter of drafting, I would strike "strike" because I am not quite sure what that means. Rather than "should strike the right balance," whatever that means, "HHS should balance the privacy and confidentiality of data with the" blah, blah, blah.

DR. FITZGERALD: Thank you. Let's read what we have now. "Stronger data security measures will be needed as more pharmacogenomics researchers access patient data. As data access and sharing expand, HHS should balance the privacy and confidentiality of personal data with access to these data for pharmacogenomics research. AHIC's Confidentiality, Privacy, and Security Workgroup should be tasked with addressing this issue."

Yes, Joseph.

DR. TELFAIR: Starting with "HHS should balance," I'm not quite sure, but it seems to me that you should have --

DR. FITZGERALD: We could say "HHS should strike a balance."

DR. TELFAIR: No, I'm agreeing with that part. I'm just saying before that there should be the way you get there. I'm not great at wordsmithing, but if the first statement is there, that is a pretty strong statement. Then something about recommending how they really should do it. It seems to me that that is what is missing before the "HHS." You have that as the third sentence, showing it should be done, but somehow or another it should come earlier as a way to get to this or a way to accomplish this, or something to that effect. "Such that" and then a statement. There seems to be [something] missing there.

DR. FITZGERALD: So you wouldn't see what we said at the end there that the AHIC Workgroup should be tasked with addressing this issue with creating that balance, with delineating the balance, with something like that?

DR. TELFAIR: Yes, I agree with the part that the balance between the two should occur. But there seems to be a bridge amiss. There is a set of bridging words between the last part of that and then moving to the tasking part. That is all I'm saying.

I apologize. I am not good at wordsmithing, so I would have to think it through. This is the sort of block that methodology people get. It's just me. But there should be some kind of bridging statement, and I'm open to people who are better at words than I am. That is just a suggestion.

DR. FITZGERALD: Yes, Julio.

DR. LICINO: I think it is not only a matter of balance because the way it states there, it is like either you have privacy and confidentiality or you do research. It is a balance between the two. In other words, if you do research you are breaking privacy and confidentiality. But I think that it should be more than that. It should be like "to ensure that

research can be conducted protecting privacy and confidentiality."

I know that sometimes there is a conflict between the two, but I think the goal should be to ensure that the research is done with full protection of privacy and confidentiality.

DR. FITZGERALD: I think we have run into this issue before because of even just how you phrase that. If you say the research should be done with protection of privacy and confidentiality, people read that as the research should be done and along the way try and protect confidentiality and privacy. Others will say privacy and confidentiality should be protected and then research can be done. You see the subtle distinction there.

So the question I think we are trying to figure out is how do you say that in a neutral way to say that both the research is done and privacy and confidentiality are protected. That has been a struggle we have had all the way along. If anybody has a better way of saying it, it would be great.

Ellen, please.

DR. FOX: Perhaps related to that is, it seems to me that there is an inadequate distinction between security and privacy and confidentiality here. It seems almost to equate the two. Is this really supposed to be about data security? Then we could maybe just get rid of "privacy and confidentiality" and talk about balancing data security against access, which is a balance. You want to maintain privacy and confidentiality, but data security, if you are going to provide access, there is going to be a give-and-take there.

DR. FITZGERALD: Right. I understand that. I think the idea was to try and say why do you need data security, in part for privacy and confidentiality reasons. But, yes.

DR. FOX: But you always need data security, even if you are not keeping something confidential.

DR. FITZGERALD: Right. So here, again, up at the top it says "protection of personal information." So the emphasis is more on privacy and confidentiality than data security.

DR. FOX: The first sentence starts with data security.

DR. FITZGERALD: I'm not saying we didn't.

DR. FOX: Oh, okay. I assumed it was the opposite.

DR. FITZGERALD: Julio, go ahead.

DR. LICINO: The issue about research is, there may be a security breach, of course, and then that destroys privacy, but in the context of conducting research you may have information that makes the person identifiable. I think that is the big issue.

DR. FITZGERALD: Yes, exactly.

DR. LICINO: You can break into a database and that is a big issue, but we are not discussing that here.

DR. FITZGERALD: Right. It is bigger than just that. Absolutely. Is that not coming [through]? We are still working.

Should we look and see what we have? No. Go ahead, Jim.

DR. TELFAIR: I actually like Paul's [suggestion to] balance those two. I think that does remain not open to the interpretation that we are doing one and the other is an afterthought, and I think in truth it is a balance. There are issues that need to be balanced. Absolute privacy would preclude research, and absolute openness would preclude privacy. Thus, it is a balance. So I like the way Paul put it.

DR. FITZGERALD: So we have now two balances, "on how to balance the need to balance"?

[Laughter.]

DR. FITZGERALD: Let's try this and see what people think. "Stronger data security measures will be needed as more pharmacogenomics researchers access patient data. AHIC's Confidentiality, Privacy, and Security Workgroup should develop guidance on how to balance the protection of privacy and confidentiality of personal data with access to these data for pharmacogenomics research."

Robinsue, yes.

DR. FROHBOESE: I'm sorry to go back to this, but I want to again just pause and think whether AHIC's Privacy and Confidentiality Workgroup is the best vehicle to look at this. I raise it for a couple of reasons. One, there are plans that AHIC will be phased out next fall and there will be a successor organization that will be stepping in for AHIC. So I just don't know the continuation of that workgroup.

Marc knows this better than I, so I would like you to address it, but it certainly has its hands full right now with looking at within the context of electronic health records, looking at all of the privacy and security aspects. Is this the right group to give this very important issue the kind of expedited attention that it needs.

DR. TUCKSON: How about if we do it this way, then, just so we can move this along. I think you are right. AHIC's future is questionable; there is no question about it. We don't know what is going to happen with it. Maybe you could say, "Through mechanisms such as AHIC," and that way you signal where you are headed. You are trying to decrease the redundancy that Barry is worried about, but you don't lock in.

Let's try to bring this one to closure.

DR. FITZGERALD: Steve and then Martin.

DR. TEUTSCH: I think part of the problem is this focuses on how to balance them rather than assessing what the right balance should be. The question really is we have to recognize tradeoffs and we need to figure out where it needs to be, and this focuses mostly on mechanisms.

DR. FITZGERALD: Martin?

MR. DANNENFELSER: I just think that the way this is worded it might sound like it is a 50/50 thing, and I think that is not the right balance, if you will. I think we should maybe take the word "balance" out and do something on how to protect the privacy and confidentiality of personal data. That doesn't mean that you are going to have 100 percent success in doing that, but that is what you are striving to do.

DR. FITZGERALD: Well, we are having a pushback on "balance."

DR. WILLIAMS: Balance doesn't mean 50/50.

DR. FITZGERALD: Martin?

MR. DANNENFELSER: I still think it sounds like we are not giving appropriate consideration to the privacy.

DR. FITZGERALD: Of course, when we say "appropriate," what is appropriate.

DR. WILLIAMS: There are two issues here. This is not the only group that is assessing this issue of personal privacy. We are discussing it in the context of the databases for pharmacogenomics research, so it is really in an informatics context. So this is not taking place

in the vacuum of no other discussion about how we weigh privacy and confidentiality versus the ability to do research.

I think what we are really talking about here is that there is an informatics component that is inextricably linked to doing pharmacogenomics research, and what we are trying to address, as I see it, in this is that at the present time the sense of the group is that we don't necessarily have those specific issues addressed for these types of pharmacogenomic databases that are being proposed.

It was news to me to hear that AHIC may be going away, but that is the way of things. But to address the issue, yes, they do have a lot on their plate, but it is within the Secretary's purview, that being an advisory committee, to tell them what to do and when to do it.

DR. FITZGERALD: So, what would you recommend? Are you happy with this?

DR. WILLIAMS: I am happy with it as it is currently constructed.

DR. FITZGERALD: Let me just go through it one more time. "Stronger data security measures will be needed as more pharmacogenomics researchers access patient data. HHS, through mechanisms such as AHIC's Confidentiality, Privacy, and Security Workgroup, should develop guidance on how to balance the protection of privacy and confidentiality of personal data with access to these data for pharmacogenomics research."

I'm looking, I'm looking, I'm looking. All right?

[No response.]

DR. FITZGERALD: We are good. Thank you very much. Thanks for all the good input.

Now we are on to No. 8A, which is on page 56 of your report. This is population stratification in drug response and some of the questions there.

"Because genomic factors may be more meaningful predictors of drug response than race and ethnicity categories, FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response."

It is a very specific recommendation to address a relatively specific problem. Everybody is comfortable with this and the wording? Joseph? Wait. Joseph and Alan. Sorry, Alan.

DR. GUTTMACHER: Better than what?

DR. FITZGERALD: I'm sorry?

DR. GUTTMACHER: Better than what? In the last sentence.

DR. FITZGERALD: "That may better explain." Better than what we have now.

PARTICIPANTS: Better than race and ethnicity.

DR. FITZGERALD: Oh, yes. Better explain differences than using race and ethnicity as explanatory factors.

DR. GUTTMACHER: If others feel that that is clear in context, then I will withdraw my question. I'm not sure it does.

DR. FITZGERALD: Joseph?

DR. TELFAIR: I guess mine is not quite the same, but it is on a similar pathway of thinking. Race and ethnicity are not biological categories, so it is not appropriate to categorize them in that way. They are more sociological categories. So if you are going to use

biological categories, I think you really do need to have a little bit more explanation at the end as to what you are going to do.

DR. FITZGERALD: So again, you are not going to help me with the wordsmithing because you don't do that.

[Laughter.]

DR. TELFAIR: Because I'm not a biologist. That is not my area of thought. To explain differences, you can talk about other differences but differences that --

DR. FITZGERALD: How about if we do this. "Encourage the collection of genetic and other biological factors such as biogeographical ancestry that may better explain differences in drug response"?

DR. TUCKSON: I think one of the key words here, and it may be overly simplistic but to answer the first question, "that may better explain individual differences in drug response." It is drug response of the individual that you are concerned about, not the differences in the social class of the patient.

DR. TELFAIR: I guess I would agree with that language because that is actually what I'm searching for. Even though these categories are there, they are actually sociological group definitions. If the outcomes are more individualistic, then you need to say they are more individualistic.

DR. FITZGERALD: Although there will probably be inclusion of data from such categories as biogeographical ancestry, which is not race or ethnicity but just ancestry.

DR. TELFAIR: Right, yes. I would agree with that.

DR. FITZGERALD: Now I have Mara and Paul and Andrea. No, not Andrea? Just Mara and Paul.

MS. ASPINALL: I think, Kevin, I was going to agree with you to put it into a sociological category such as race and ethnicity, and I don't know what you do with gender, whether you put it in there. But I thought that would be useful, to categorize it in bunches and use race and ethnicity as an example.

DR. FITZGERALD: Maybe "more meaningful predictors than social"?

MS. ASPINALL: I would also do it in the first sentence.

DR. EVANS: "Than less exact proxies," something like that. The whole point of this is that these aren't very good proxies.

DR. BILLINGS: But they are not also exclusive proxies for the individual. The population genetic factors, as well as socioeconomic or others, at the individual level and at the group level may be co-explanatory. So I think you are looking, rather, for things that are better. You are looking for things that are more comprehensive descriptors, aren't you?

MS. ASPINALL: Isn't it both?

DR. BILLINGS: I'm saying both.

DR. FITZGERALD: So again, recommendations for words? Take a look at what is up there.

DR. BILLINGS: I wouldn't say "more meaningful predictors." I think they are predictors, for instance.

DR. FITZGERALD: Wait a minute. I need concrete suggestions here. Mara.

MS. ASPINALL: Let me first understand. Is Warfarin an example of this, where race and ethnicity and age only explain 25 percent of the variables but when you put in genomic

factors you then explain 75 percent of the variables? Is that the idea?

DR. WILLIAMS: My interpretation, as I read this, was that we know that some drugs are coming to market using race and ethnicity as defining [factors.] BiDil is really the example of this. What we are trying to say is that genomically that doesn't make sense because within a self-identified group of African Americans there is a dramatic difference in response based on the genomic factors, which in fact give you a deeper level.

So I think it addresses a current issue, which is that these things are being used as proxies for development of drugs for subgroups and it recognizes that that is a reality, but we are saying we need to move beyond that.

DR. FITZGERALD: Paul.

DR. BILLINGS: I actually disagree. I agree with what Marc just said, though. I think that in the end socioeconomic class and the biological factors will have something to do with who takes the drug and how they respond.

DR. FITZGERALD: Right. I think the question is, is the sociological, economic data that is relevant captured by categories such as race and ethnicity. That is one of the questions.

Now, Gurvaneet.

DR. RANDHAWA: I think some of the confusion here is we don't qualify what predictor. If you are saying a biological predictor, I don't think there is any argument. If you are talking about a predictor to a treatment, then there are non-biological factors that [affect] this completely. So I think if you say "biological" to the predictor, that is better.

DR. FITZGERALD: I think one of the concerns here is that categories such as race and ethnicity, which everyone acknowledges are socioeconomic categories, are not even perhaps the best socioeconomic categories to use, right?

Go ahead. Mara and Jim.

MS. ASPINALL: I don't see them as socioeconomic categories.

DR. FITZGERALD: What kind of categories are they?

MS. ASPINALL: I wouldn't put "economic" in. I think it is sociological. While I think that is important, it has nothing to do with economics. They are sociological categories.

So I guess I would make two suggestions. At the beginning of the first sentence, although maybe it changed now -- sorry. It changed again.

DR. FITZGERALD: I know. It is evolving.

MS. ASPINALL: I had some words there. Anyhow, I don't think it should be "socioeconomic." It should be "sociological."

DR. FITZGERALD: Right. "Sociological." That's fine.

MS. ASPINALL: Secondly, in terms of Marc's comment, I understand BiDil, but to me Warfarin, which is also very current, is exactly this issue. It has been dosed based on race, ethnicity, age, and weight, and now it can be dosed on those and genomic factors.

DR. EVANS: There are major differences in response to Warfarin by race, and it turns out that VCOR and SIP explain most of that.

I think, if we go back to the original 8A that is in our book, that artfully dodges the contentious issue of defining race. Is it biological, is it all social construction. We don't need to get into that, and I think we would be foolish to tackle it.

I think 8A says genomic factors may be more meaningful predictors of drug

response than proxies like race and ethnic categories. Therefore, we should encourage collection and analysis of genetic and other biological factors. That doesn't say that race is some biological issue that may better explain differences.

I think that really is -- I didn't design it, so I can say this -- an artfully worded recommendation.

DR. FITZGERALD: Are you saying we had all this discussion for nothing?

DR. EVANS: Yes.

DR. FITZGERALD: No, no.

[Laughter.]

DR. FITZGERALD: Look up on the screen and see, people, if what is up there captures things more adequately than what we had or what we had is closer.

We have right now, "FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be more meaningful predictors of individual differences in drug response than sociological categories."

DR. EVANS: No.

DR. FITZGERALD: No. That doesn't do it. Cross that out.

DR. EVANS: What this does is it lends --

DR. FITZGERALD: Wait a minute. I have Michael, Martin, and Jim. Michael.

DR. AMOS: So, isn't the problem really when you try to use race and ethnicity as a biological marker? That is the problem, right?

DR. EVANS: Well, when you try --

DR. FITZGERALD: Wait. I have to keep other people in here.

DR. AMOS: You run into problems when you try to use race and ethnicity as a biological marker.

DR. FITZGERALD: So, what are you recommending for the recommendation?

DR. AMOS: Joseph.

DR. FITZGERALD: I see.

[Laughter.]

DR. FITZGERALD: Martin, go ahead.

MR. DANNENFELSER: I thought that, for the one that we just had up there a minute ago, if we just put "e.g." in parentheses at the end for the sociological factors and then just put race, ethnicity, gender as examples.

DR. FITZGERALD: Martin, you got it. Help us out here again. What are we doing?

MR. DANNENFELSER: The formulation we just had before we flipped back there. Where it ended was "sociological factors" or something. Then at the end of that, after "factors," put in parentheses, "e.g. race, ethnicity, gender."

DR. EVANS: But again, now you are jumping right into the controversy. Can I talk or not?

DR. FITZGERALD: I just want to make sure I get the suggestion right, that's all, before we comment it.

DR. EVANS: Gender is not a sociologic definition. I don't think we should --

PARTICIPANT: Yes, it is.

DR. EVANS: Well, sex is not.

DR. FITZGERALD: Wait a minute.

DR. AMOS: I can give you the words.

DR. FITZGERALD: Hold on. Let's see what people think about this. So we are still not comfortable. Michael, what were you thinking?

DR. AMOS: I was thinking that "differences in drug responses than when attempting to use sociological factors as biological markers."

DR. FITZGERALD: "In drug responses than when using sociological factors as biological markers." "FDA should develop guidance that encourages the collection and analysis of," "that may be better predictors of individual differences in drug response than when using sociological factors as biological markers."

We have a new recommendation up there. Now I will take comments and questions. Joe, you are first.

DR. TELFAIR: Instead of "as biological markers," just use the word "as proxies." Take out "biological markers" and use "as proxies."

DR. FITZGERALD: Next comment, anybody? Yes.

DR. EVANS: I will make one more stab at this. This last sentence as it stands defines, for example, gender as a sociological construct. It is both a biological and sociological construct, as many would argue race contains both. Therefore, I don't think that is accurate. You can say something like "in drug responses when using broader categories" or "broad proxies such as race, ethnicity, gender." How about just "when using broad proxies"?

DR. FITZGERALD: "When using broad proxies."

DR. EVANS: Then we can avoid this fruitless debate which inflames everyone as to how do you define these things.

DR. AMOS: Yes. "When you attempt to identify biological differences." Jim? "When you attempt to identify biological differences."

DR. EVANS: I think "broad proxies." Then you don't need to get into it.

DR. FITZGERALD: Wait a minute now. That you like? All right. Everybody take a look at what we have. Door No. 3. No, it is still changing.

Here we go. "FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be better predictors of individual differences in drug response than broad proxies, e.g. race, ethnicity, and gender."

I have Martin and Gurvaneet.

MR. DANNENFELSER: Is the word "categories" better than proxies? I don't know; "proxies" to me sounds a little inappropriate there. They are not necessarily proxies. I think they are just different ways of categorizing.

DR. FITZGERALD: We have a "categories" suggestion. Gurvaneet seems to be on that, too.

DR. RANDHAWA: I agree with that. I think, if I was a pharmacoepidemiologist looking at this recommendation, I would not agree with this because if I'm looking at sociological databases and I'm saying such and such of Race A has a better response, it may be because of access or whatever else.

But it may have a much bigger predictor than any genomic factor. So then you are saying better predictor. It is not quite true here. It may be a better predictor for a biological response but not a better predictor of a drug response because the drug response has many other

factors and biology is just one part of it, sometimes a very small part of it.

So unless you make it clear that it is a biological predictor and not a predictor per se, I don't think the statement is true.

DR. FITZGERALD: I guess one of the problems with race and ethnicity is they are usually self-assigned.

DR. RANDHAWA: It doesn't matter because you are looking at it from an effectiveness point of view. Someone who is not going to respond to a drug, whether it is because you can't buy a drug, you can't afford to have a complete prescription of the drug, or because your genomics are not good enough, it doesn't really matter. But if you are looking at it from a purely biological phenomenon, then that is a different issue.

DR. FITZGERALD: What was your suggestion about the recommendation? How do you want to change that?

DR. RANDHAWA: It is fine when you put "biological" in there.

DR. FITZGERALD: Good. Joe?

DR. TELFAIR: I would actually concur with that because that is really what my original thought was trying to get around.

DR. FITZGERALD: Steve.

DR. TEUTSCH: Rather than "proxies," which is pretty vague, I would probably talk about sociodemographics.

PARTICIPANTS: No.

DR. FITZGERALD: "Categories"? I thought that was going to go to "categories." "Categories."

All right. We are going to try this.

DR. WILLIAMS: I would just point out that it does say "maybe."

DR. FITZGERALD: We are not going to try this.

DR. WILLIAMS: It doesn't say "is." It says "maybe."

DR. FITZGERALD: Martin is back on.

MR. DANNENFELSER: It is just a real fine-tune here. Maybe at the end, rather than "e.g." we could just say "broad categories like."

DR. FITZGERALD: "Such as"?

MR. DANNENFELSER: Or just "broad categories like."

DR. FITZGERALD: Oh, I see.

MR. DANNENFELSER: Because a lot of other things could be in categories besides race and gender. There are all kinds of categories. I just want to make it sound like "categories" refers to those types of things.

DR. FITZGERALD: We are going to try another time here. Let's try this. "FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be better biological predictors of individual differences in drug response than broad categories such as race, ethnicity, and gender."

Are we happy with that?

[No response.]

DR. FITZGERALD: That's wonderful, because now I'm going to go to the next one, 8B. I'm going to turn this over to Reed because I'm going to go get a drink.

[Laughter.]

DR. TUCKSON: Population stratification in drug response, recommendation 8B. "When drugs are shown to be effective in certain racial and ethnic subpopulations (e.g. BiDil), FDA should encourage manufacturers to conduct additional post-market studies to identify biological, social, behavioral, and environmental markers that may underlie the differential drug response."

The floor is open.

DR. AMOS: Reed? Following on to the last discussion, I think you should say "genetic."

MS. ASPINALL: In the end. Instead of the whole list, just "identify genetic markers."

DR. AMOS: No, other things, too. Just "conduct additional post-market studies to identify genetic, biological, social." Just add that to the list because what we are saying in the one before is that this might be a better predictor.

DR. TUCKSON: Do you see a difference between "genetic" and "biological"?

PARTICIPANTS: Yes.

DR. TUCKSON: So you have genetic, biological, social, behavioral, and environmental.

DR. WILLIAMS: I would object to that difference. I think "biological" is broader, but genetic is biological and to have both of them implies that genetic is some other, non-biological thing floating out there.

DR. TUCKSON: Mara.

MS. ASPINALL: I'm not going to get into the last debate. Maybe somebody could help me. There aren't many --

DR. TUCKSON: I'm sorry, Mara. Let me just get this one nailed. Wait a minute. So, are we adding "genetic" or not?

PARTICIPANTS: No.

DR. TUCKSON: So we are not adding "genetic."

DR. WILLIAMS: Two points. I completely agree with what Alan said, but in the previous one we did specifically articulate "genetic and other biological." So from a language consistency perspective between the two recommendations, that would be one point.

DR. TUCKSON: So "genetic and other biological."

DR. WILLIAMS: The second point is that this is a pharmacogenomic report, and so it probably should be explicitly stated.

DR. TUCKSON: So, "genetic and other biological." Thank you. Mara?

MS. ASPINALL: I was exactly where Marc was, "genetic and other biological." But maybe somebody can explain where social, behavioral, and environmental come in in this one where they hadn't previously come in at all. I guess, to make it consistent, I like "genetic and other biological that may underlie the differential drug response," and not to add the other three.

DR. TUCKSON: This is a fundamental difference of opinion here as to whether or not you say that we would get beyond the biological to include behavioral and environmental.

DR. TEUTSCH: I think this talks about effectiveness, not simply the biological response. It gets back to what Gurvaneet said. When you have effectiveness, that takes into lots of consideration these other things are very germane to that, rather than simply a biological

phenomenon.

DR. TUCKSON: Mara, I appreciate your having raised it. Now we are beginning to see that the key word to focus in on is "effectiveness" and many different determinants of effectiveness other than the biological issues and that they want to open it up to include all of those, which is post-marketing stuff, which is terrific.

With that we have it. We will move on. No? Sure.

DR. WILLIAMS: I would suggest we add the word "more" before "effective" in the first line because otherwise there is no differential drug response, which we refer to at the end.

DR. TUCKSON: So, "when drugs are shown to be more effective in certain racial." Good. Sounds like a friendly amendment. Any last ones? Yes.

PARTICIPANT: I agree with what you just said about the difference in response and effectiveness. Should we change the very last word to "differential effectiveness"?

DR. TUCKSON: So the response is too narrow. "Differential drug" --

PARTICIPANT: "Effect," because of what Steve was talking about. That encompasses it.

MS. ASPINALL: That deals with my discomfort as well because it broadens it at both ends.

DR. TUCKSON: So, "drug effects," or "effect," either one you want.

Good. Anyone else? Say again?

DR. AMOS: Does "response" include safety and effectiveness? Because we are talking about safety here as well. It is the same?

DR. TUCKSON: It is being said effects are both positive and negative. Good question. Thank you.

All right. With that, we will move to the next one. Take it back, sir, freshly hydrated.

DR. FITZGERALD: Let's make sure everybody agrees with this one. No. 8B, "When drugs are shown to be more effective in certain racial and ethnic subpopulations (e.g. BiDil), FDA should encourage manufacturers to conduct additional post-market studies to identify genetic and other biological, social, behavioral, and environmental markers that may underlie the differential drug effects."

DR. TUCKSON: There is one thing I just realized. Although we did it for discussion, do we need the "e.g. BiDil"? What that does is to single them out.

DR. EVANS: It also has never really been compared head-to-head.

DR. TUCKSON: Yes. Let's leave the example out.

DR. EVANS: Jettison it.

DR. FITZGERALD: So we are going to take out "BiDil" now.

Everybody good? We are all set. Fantastic. Next.

DR. TUCKSON: Process check. We are at Gatekeepers section.

DR. FITZGERALD: We are moving. So when is the break?

DR. TUCKSON: There is none.

DR. FITZGERALD: No break? There are no breaks.

DR. TUCKSON: There is no break until we do a better calculation of whether we are going to make it.

DR. FITZGERALD: Here we go. Gatekeepers. Now, just to give you, again, a brief overview, these are the entities that can enable, halt, or redirect the course of pharmacogenomic technologies, effects integration, and patient access. These are the four groups that were identified. I'm not going to go through all the roles of each because you are all familiar with those. Let's go right to Recommendation No. 9, Slide 58.

DR. FERREIRA-GONZALEZ: Can I make a comment on that?

DR. FITZGERALD: Sure. A comment on what?

DR. FERREIRA-GONZALEZ: The Gatekeepers section. We have the role of the industry, the role of FDA, the role of CMS, and we have the role of the laboratories performing the testing, which are regulated through CLIA. Even though it might be a role of CMS, the way it is listed here CMS has a role of coverage and reimbursement. That needs to be moved earlier in the section or actually highlighted because I think it is a very important gatekeeper.

DR. FITZGERALD: Which slide are you on, No. 56?

DR. FERREIRA-GONZALEZ: Either. On No. 53 you have gatekeepers. You have industry, FDA, CMS, and other third-party payers. CMS should have, maybe, two bullets because it has different roles through the CLIA.

DR. FITZGERALD: So you want to change the text of the report. Why don't you write up that suggestion and give that to Suzanne to change the text. It is not going to change Recommendation No. 9 yet, though, right?

DR. FERREIRA-GONZALEZ: No.

DR. FITZGERALD: So we are going to Recommendation No. 9.

DR. TUCKSON: I will give you the language. It is Slide 56, the role of CMS and other third-party payers. "Reimbursement may not be perceived to be adequate"?

DR. FITZGERALD: Again, if you give that to Suzanne, we will take care of that. We are going right to the recommendation, as you would order us.

All right. This is Recommendation No. 9. It is found on page 74 of the report. This is on reimbursement.

"In clinical situations where a pharmacogenomics test has been shown to enhance safety and/or effectiveness of clinical management (i.e., has demonstrated clinical utility compared to alternative management strategies) and provides value comparable to or an improvement over other covered services, public and private health plans should provide coverage and reimbursement for the test and the most clinically appropriate drug as indicated by pharmacogenomic test results."

Marc, then Paul, then Joseph.

DR. WILLIAMS: This has major scope issues. We are recommending to the Secretary. The Secretary only has purview in terms of reimbursement over CMS-related payers. So that would be Medicare and to some degree Medicaid. So any reference to private health plans in this, we can all feel that way but it is not within the scope of what we can recommend to the Secretary.

The second point I would make that I think has been missed in this recommendation that is really critically important is the idea that what we really should be recommending to the Secretary is that clarification be forthcoming from CMS as to whether or not pharmacogenomic testing is going to be considered to be a preventive service and thereby

not covered by CMS. The legislation basically excludes that without modification or, as at least there have been some rumors, it will be considered in the context of the disease, in which case it would be covered.

That is the critical issue that I think this recommendation needs to address, that the Secretary clarify with CMS how these tests will be treated by CMS, if that is a fair statement to Barry.

DR. FITZGERALD: Just a point of clarification. Suzanne, go ahead.

MS. GOODWIN: Well, I suppose two points of clarification. The first one, that recommendation is in the Coverage and Reimbursement Report, and I think we do in the text of the report reference that particular recommendation.

I know at one point during the development of these recommendations we did have a specific one saying exactly what you said and reiterating what the Coverage Report says, and after discussion amongst the taskforce it was decided that it would not be included in this set of recommendations. Personally, I am not recalling the discussion why it was in there.

DR. WILLIAMS: I'm sorry. This is specifically to ask for the clarification about how these pharmacogenomic tests will be considered by CMS. Is that what we are talking about?

MS. GOODWIN: Yes.

DR. WILLIAMS: If it is in the Coverage and Reimbursement Report, I think we should --

MS. GOODWIN: Oh, I'm sorry. Not specifically to do with pharmacogenomics. The recommendation that was in this report asked for clarification how the screening exclusion policy of CMS applies to PGx tests.

DR. WILLIAMS: Well, again, my personal opinion is I think it absolutely has to be in here.

DR. FITZGERALD: I have Paul, and then Joe, and then Barry and Marc.

DR. BILLINGS: In this particular one, I would prefer to take out the clause "comparable to or improvement over other covered services." This would allow for this to have to do with comparison to other covered services or de novo improvements. In other words, as long as they deliver value, what do we care if it is covered before or not.

Secondly, I would like to see the word "adequate reimbursement," or some other modifier of "reimbursement," be put in there, since we all know that coverage and reimbursement can be inadequate.

Then, finally, that --

DR. FITZGERALD: On that second one, where would you put "adequate"?

DR. BILLINGS: "Adequate" before "reimbursement."

DR. FITZGERALD: Before "reimbursement." Thank you.

DR. BILLINGS: Then, finally, to what Marc just said, it is true that we can only recommend policies that could be implemented CMS, but we could hope or we could wish that, as some payers do follow CMS protocols.

DR. FITZGERALD: That I think was our intent in drafting it.

DR. BILLINGS: You might even say that.

DR. FITZGERALD: I have to check my list here. Mara. Oh, Joseph was next. I'm sorry. Joseph. Sorry, Mara.

DR. TELFAIR: It is okay. I actually was agreeing with Paul the Lesser on the second comment that he made. That was going to be part of mine. So I would just agree with that.

DR. FITZGERALD: Thank you. Mara and then Barry.

MS. ASPINALL: I also agree with what Paul had said, but I'm struggling with the beginning piece about "in clinical situations." By definition, if it is already in a clinical situation, there either will have been reimbursement or coverage or not. So I don't think we need that phrase at the beginning.

DR. FITZGERALD: Just start with "where."

MS. ASPINALL: Right. That was number one. Number two is, does it need to meet a standard above, "when it says to enhance safety or effectiveness of clinical management" or to show effectiveness of clinical management? I didn't know what the intention was there; that it is above a standard of what existed now?

DR. FITZGERALD: Right. In order to change reimbursement policy.

MS. ASPINALL: Let me come back to that.

DR. FITZGERALD: Barry.

DR. STRAUBE: I have to agree where Marc was headed. As written here, it is again possibly a meaningless recommendation because we are governed by statute in terms of how we cover things. Safety and effectiveness is the way coverage decisions used to be made under HCFA back before 1995. Anything FDA-approved as safe and effective was covered.

That is not the case anymore. "Reasonable and necessary" we are struggling with trying to once again define. We are getting comparative effectiveness, let alone possibly cost effectiveness, that is slowly starting to work its way in.

Making a coverage decision is the way I am reading this. It is almost instructing us. We don't use value. That is not anywhere in terms of coverage decision policy.

We are already starting to do this. That is why I'm here today struggling with this issue of if the law says screening is never covered, if the law says prevention is but it has to be enacted by Congress, could we somehow construe this to be a diagnostic test linked back usually to symptoms or physical findings but possibly to family history and to other entities.

So there is a whole way of approaching this that could be extra-statutory or could be requiring a statutory approach. When you read the preamble and everything else that leads up to this recommendation, people are struggling with how do we change the Medicare program in particular to even allow us to make a coverage decision. It has nothing to do with value.

DR. FITZGERALD: Do you have a recommendation for how we can reword this?

DR. STRAUBE: Well, again along the lines of what Marc was saying.

DR. FITZGERALD: Take a look at what we have. Where we are at the moment is, "When a pharmacogenomics test has been shown to enhance safety and/or effectiveness of clinical management (i.e., has demonstrated clinical utility compared to alternative management strategies) and provides value, CMS and other federal health insurance programs should provide coverage and adequate reimbursement for the test and the most clinically appropriate drug as indicated by pharmacogenomics test results."

Is that closer; is that further? I'm going to do Marc and then Mara.

DR. WILLIAMS: I think this gets at the point that Barry was making. You are

basically telling Medicare how to make its coverage decisions and you are using language that is not consistent with the CMS language on how they make those coverage decisions.

I would default back to a recommendation that would state that the Secretary explore with CMS the issue of whether pharmacogenomic tests will be excluded from coverage based on screening or prevention language or whether there are non-statutory solutions that would allow consideration of coverage using the usual mechanisms under which CMS operates.

I think that is what we can actually tell the Secretary that can actually be accomplished by a DHHS group.

DR. FITZGERALD: Reed and then Mara.

DR. TUCKSON: I don't want to struggle with the word "adequate." Once you start putting those kind of words in this kind of thing, you open up enormous contractual issues and debates and fighting and so forth. I just think you reimburse it. The adequacy is perceived by whoever it is perceived by.

DR. FITZGERALD: Where was the adequacy part? That was in front of "reimbursement," right? You want "adequate" struck.

DR. TUCKSON: Right.

DR. FITZGERALD: I have Mara and then Jim.

MS. ASPINALL: I'm closer to where Marc was. Before I wordsmith, but I understand the need, I want to take it up a level. Was the idea here the fact that if there are tests for which pharmacoeconomics relevant, useful -- I'm not using the perfect words here -- we want them covered? That is what I'm struggling with.

There is not a comparable piece. The headline is reimbursement for pharmacogenomic products. The recommendation only talks about reimbursement for pharmacogenetic tests. So my first question is, is there an assumption that if it is a pharmacogenomic-related drug it will be reimbursed? That is probably not a terrible assumption, but I'm assuming that that is there.

So I wanted to get it up a level to not get to quite so much detail but rather say the group is in favor of tests that are pharmacogenomic, that are related to tests that are related to drugs that have gone through this process that we have outlined in the other recommendation. HHS should find a way to cover these because, by definition, if we have done all this, we have shown the basic research, we have shown the translational research, and then the test isn't covered, there will be no incentive to create these tests beyond that basic research.

DR. FITZGERALD: Reed has a question. Go ahead.

DR. TUCKSON: Let's take it outside of this for a minute and let's talk about all the manufacturers of nuclear imaging machines. At the end of the day, does CMS have to cover every new nuclear imaging machine out there?

In this case, does this open the door to no matter what it is? Let's say you have a great test for a drug that CMS may say is beyond the realm of the formulary today. Does this open the door to everything being open on the table now?

MS. ASPINALL: I look at it as it may be different options for the same thing in the same way that many different drugs are approved for the same condition. The way this is going with pharmacogenomics, my suspicion is actually there won't be multiple tests initially. A test for X condition is covered and there may end up being three tests for X condition, but the patient only needs to go through it once. So the market may go to the lowest-price one.

Indeed there may be five manufacturers of nuclear imaging machines. A hospital only needs one, they choose the one they want, and that test or that machine is covered to get the answer to decide who best or how best to use that particular drug.

I guess I'm saying there might be multiple tests but each patient only needs one.

DR. WILLIAMS: I think I can clarify this.

DR. FITZGERALD: I hate to tell people; we are only a little over halfway through.

DR. WILLIAMS: The specific language that we are dealing with, without naming it as such, is really addressing the issue of the formulary. At the present time, pharmacy benefit managers and health managers use formularies to try and control cost. If you have compelling data that shows that a certain individual would benefit from a certain drug, then are formularies really appropriate.

Again, getting back to what CMS can do, under Medicare Part D and to some degree Medicare Part C, if there was compelling evidence that there were pharmacogenomic differences let's say within the SSRI category, CMS could say to its contractors we are not going to allow you to apply a formulary to this class of medications. You need to consider medical necessity based on the pharmacogenomic information that will lead to best dosing.

So the issue is that we are kind of talking around the issue. "Clinically appropriate drug" is really referring to the idea that there is a best drug that could be identified for an individual and getting away from using formularies.

DR. TUCKSON: I'm going to be real quick because the moderator is moving us forward. I just want to make sure that this does not get read as just because you can come up with a terrific pharmacogenomic test and match it to a drug therefore CMS is obligated to cover that test and that drug when they may not have been willing to cover that drug in the first place.

DR. FITZGERALD: I have Jim and Barry and Chira. We are going to be here forever. Go ahead. Let's focus on getting a recommendation.

DR. EVANS: I understand. I think Barry's points are really well taken. It would be silly of this Committee to make recommendations that can't be enacted or are not under the purview of CMS.

I just have a question. Is there any utility in this Committee to suggesting a categorization for pharmacogenomic tests, for example as diagnostic tests, that would short-circuit some of this and make them covered or coverable more easily when they meet criteria in improving efficacy and effectiveness? That is my question, basically for you, Barry, I guess.

DR. FITZGERALD: Barry, go ahead.

DR. STRAUBE: I'm not sure I understand the question.

DR. EVANS: Could there be any utility in us making a recommendation about how to categorize pharmacogenomic tests that would then allow more action or leeway on the part of HHS?

DR. STRAUBE: I was going to suggest a slightly different thing, and I'm not paying attention to this language at all. It would be to recommend to the Secretary that he ask CMS to produce a guidance document on current status of genetic testing as it relates to pharmacogenomics, including surveying the private sector to see what coverage was extant in that setting and to make some recommendations to him as to what options were available. Something of that nature.

DR. EVANS: Maybe say with the intent of being able to cover improved tests or improved use of drugs.

DR. FITZGERALD: Here we go. Let's take a look. "CMS should clarify how the Medicare screening exclusion policy applies to pharmacogenomic tests" -- no. That is not it. Try it again. Barry, do it again.

DR. STRAUBE: This Committee recommends to the Secretary that he request --

DR. FITZGERALD: Hold on, hold on. "This Committee recommends to the Secretary." Go ahead.

DR. STRAUBE: That he request that CMS produce a guidance document.

DR. FITZGERALD: "CMS should produce a guidance document.

DR. STRAUBE: Detailing current coverage issues pertaining to pharmacogenomics in the Medicare program, including surveying the private sector for what is currently covered extant there.

DR. FITZGERALD: Hold on. "Pertaining."

DR. STRAUBE: Forget the "extant."

[Laughter.]

DR. FITZGERALD: Keep watching what is going on in that lower paragraph, and we will keep working on this as Suzanne tries to get it down.

"CMS should develop a guidance document detailing current Medicare coverage issues pertaining to pharmacogenomics tests." No?

MS. ASPINALL: No, "pharmacogenomics."

DR. FITZGERALD: "Pharmacogenomics."

MS. ASPINALL: "Pharmacogenomic coverage" as opposed to just tests, because we have issues as to whether drugs are going to be approved as well.

DR. FITZGERALD: So, "detailing current Medicare coverage of pharmacogenomic drugs and diagnostics"?

MS. ASPINALL: No.

DR. FITZGERALD: No. Just "pharmacogenomics." "Detailing current Medicare coverage of pharmacogenomics," period. Everybody is good with that? Okay. Next.

DR. STRAUBE: "In doing so, CMS should survey the commercial sector policies and should identify future coverage issues." We can word that better.

DR. FITZGERALD: Now that, I'm presuming, is all you are suggesting in this. So the whole top part can get tossed.

MS. GOODWIN: Can I ask, what is the commercial sector policies you are talking about? Private health plans.

DR. STRAUBE: Yes.

MS. GOODWIN: What is the purpose of that survey?

DR. STRAUBE: To see what the current coverage policies are so that we can compare that to restrictions under Medicare and try to get them in alignment, if possible. We are going to find that they are different. Whether they are grossly different or not remains to be seen.

DR. WILLIAMS: That is actually be done in the area of cytogenetics and molecular diagnostics as we speak. So that is very consistent with the direction that CMS has been taking.

MS. ASPINALL: There was some interesting private sector work looking at the total cost of treatment with the addition of pharmacogenomic tests reducing the full cost of treatment.

DR. FITZGERALD: So [this is] what we have here currently. Everybody take a look so we can move on with this. "CMS should develop a guidance document." No, actually before that, "The Secretary of HHS" -- how did that begin? "CMS should develop a guidance document detailing current Medicare coverage of pharmacogenomics. In doing so, CMS should survey private health plan policies and should identify future coverage issues to identify inconsistencies in coverage." We have "identify" twice here.

MS. ASPINALL: Can I ask Barry for a friendly amendment? Do we need "inconsistencies" or just "to understand current coverage"?

DR. STRAUBE: We need to understand current coverage and also, again based on this Committee's report, how do we get to some of the other issues that have been raised and/or if we can't, why not.

DR. FITZGERALD: Right now everything has to be in terms of words that are going into that recommendation. I just want to be sure here. "Plans and policies to identify inconsistencies in" -- we are having problems capturing all this.

DR. STRAUBE: "Inconsistency." I'm not sure where that word is coming from.

DR. FITZGERALD: Don't get rid of "inconsistencies."

DR. STRAUBE: Do get rid of it.

MS. ASPINALL: "To identify differences in coverage between Medicare" --

DR. STRAUBE: I think, again the differences are not the primary issue. The real key issue is what can we cover or not right now. If we can't cover anything in terms of tests, we can cover the medications.

DR. FITZGERALD: Let's just focus on you putting words up on the screen so we can all agree to the words. "In doing so, CMS should survey private health plan policies to identify differences in" -- is this okay so far? "To identify differences in Medicare and private health plan coverage and future coverage issues."

DR. STRAUBE: "Identify differences in Medicare and private health plan coverage."

DR. FITZGERALD: "To identify differences between Medicare and private health plan coverage and future coverage issues?

DR. STRAUBE: Sure. I'm okay.

DR. FITZGERALD: You are comfortable with that.

DR. STRAUBE: Although I would put "Medicare coverage and reimbursement." In fact, "coverage, reimbursement, and oversight."

DR. FITZGERALD: Wait, no, we can't do oversight. Don't go there.

DR. STRAUBE: That's fine.

DR. FITZGERALD: This is what we have right now. "CMS should develop a guidance document detailing current Medicare coverage and reimbursement of pharmacogenomics. In doing so, CMS should survey private health plans to identify differences between Medicare and private health plan coverage." No? "And future coverage issues." "As well as future coverage issues."

They are happy so far. Paul the Not Often Heard From, yes.

DR. WISE: The original recommendation in the book and on the first slide was fairly generic. It wasn't about Medicare per se. We have just basically thrown all children out of the recommendation. That is fine if we want to be explicit about that, but there are still plenty of other issues that were originally part of the content for Recommendation No. 9 that are relevant to children and Medicaid.

So if move to what is up there now, which might be very helpful someplace else, the other programs need to be included to reflect fairly what was originally in the content of Recommendation No. 9.

DR. WILLIAMS: Is there any reason not to just have "Medicare and Medicaid coverage"?

DR. WISE: That was going to be my suggestion, if the Medicare types were happy with that.

DR. FITZGERALD: Barry.

DR. STRAUBE: Again, practically speaking though, we have less to say about Medicaid and SCHIP policies.

DR. FITZGERALD: But you have something to say.

DR. STRAUBE: We could comment on that, yes, how much we would have to say. Sure.

DR. FITZGERALD: So what I'm getting, then, is we have Medicare, Medicaid, and SCHIP. Next, Steve?

DR. TEUTSCH: I'm perfectly fine with this recommendation. I just am concerned that there were a number of things that came up in the report that related to how we tie utility and value to coverage of decision-making. I understand we were trying to push CMS for sure, but we actually got feedback from the private sector as well because they look to Medicare for guidance, or CMS for guidance and leadership on these issues. We [have to] somehow pull this together because there is also the influence that HHS has over the federal employee health benefits programs and others.

The concern was, by waiting for a report, which is great, it is going to be years until all of this really happens. We wanted to provide some guidance to the agencies that they should do this on the basis of incremental effectiveness and value. That was part of the intent to do that.

Now, we may decide we don't want to go there and this will suffice, but I just want to be sure everybody is clear that that was the reason that other recommendation was crafted the way it was.

DR. FITZGERALD: Marc. Again reminding everybody, we are only a little halfway through. Then Ellen.

DR. WILLIAMS: My response to that is basically I think that the CMS decisions have to be made on the statutory terms that they are given, which is necessity and reasonableness. So we can put that language in there, but it means nothing. We know that there are some overlaps between what we mean by utility and effectiveness and what you mean by reasonableness and necessity, but I think if we are going to reflect that here we need to reflect the language that CMS can actually act on within its purview.

DR. FITZGERALD: Ellen.

DR. FOX: I suggest you might want to survey public health plans as well as

private.

DR. FITZGERALD: Public and private health plans, okay. Any other comments? Gurvaneet.

DR. RANDHAWA: Just focusing on that point, I'm not sure if we focus only on differences between the plans that that is the only thing we need to get to help inform future decisions.

DR. FITZGERALD: To identify similarities and differences.

DR. RANDHAWA: I would suggest rephrasing it, instead of making it more text, just to say "to survey current coverage policies or issues to help inform future CMS coverage," and leave it at that, whether it is similarities, differences, different criteria, whatever it may be.

DR. FITZGERALD: So you would like, "In doing so, CMS should survey current public and private health plans"? "Should survey current coverage." "Should survey private and public health plans." "CMS should survey public and private health plans to identify issues"?

DR. RANDHAWA: "To help inform their future coverage."

DR. FITZGERALD: "To help inform future coverage issues."

PARTICIPANT: Decisions or issues?

DR. RANDHAWA: "Future coverage decisions."

DR. FITZGERALD: Now we have, "CMS should develop a guidance document detailing current Medicare, Medicaid, and SCHIP coverage and reimbursement of pharmacogenomics. In doing so, CMS should survey public and private health plans to help inform future coverage decisions."

MS. GOODWIN: The second sentence needs to clarify what CMS is surveying these health plans about. That was part of the language we took out.

DR. RANDHAWA: It would be coverage decisions and how they make their own coverage. That is the intent of the survey, I'm guessing.

MS. GOODWIN: About how they make their coverage decisions?

DR. FITZGERALD: "Survey public and private health plan decision-making," or whatever. Mara.

MS. ASPINALL: I like "decision-making," and end with "coverage and reimbursement decisions," so it is comparable to the first sentence.

DR. FITZGERALD: "Should survey public and private health plans about their decision-making"; is that right? "About their PGx coverage decision-making" or just "decision-making"?

MS. ASPINALL: No, just "decision-making."

DR. FITZGERALD: "About their decision-making processes" or "policies"? "Policies," maybe? "Policies," probably.

PARTICIPANT: "Processes" if it is decision-making.

DR. FITZGERALD: "To help inform future coverage and reimbursement decisions." Now we are going to try this. No, we are not. Martin.

MR. DANNENFELSER: I don't know if the "in doing so" ties as well now to that first sentence or we should just say "CMS should also survey."

DR. FITZGERALD: Just get rid of "in doing so."

MR. DANNENFELSER: Say "should also."

DR. FITZGERALD: "CMS should develop a guidance document detailing current Medicare, Medicaid, and SCHIP coverage and reimbursement of pharmacogenomics. CMS also should survey public and private health plans about their decision-making processes to help inform CMS' future pharmacogenomics coverage and reimbursement decisions." So, just their decisions or anyone else's decisions? "Its future," okay.

"CMS also should survey public and private health plans about their decision-making processes to help inform its future pharmacogenomics coverage and reimbursement decisions."

How are we doing now? Let's see. I think most everybody has been beaten into a complete stupor.

DR. STRAUBE: Kevin, as you are surveying, as a point of interest to folks, I can, in some cases with the Medicare program, ask for public comment on guidance documents. So this might include the capability of seeking public comment, too. I don't know that we want to put that into the recommendation.

DR. FITZGERALD: No, no.

DR. STRAUBE: Just so people know.

DR. FITZGERALD: Emily.

DR. WINN-DEEN: I just have a concern that by only talking about surveying people's decision-making processes we are not going to get information on their actual coverage and reimbursement. Do we want that as well as their processes? Yes, okay.

MS. ASPINALL: Yes, I think that was the intention.

DR. FITZGERALD: So we want what now?

DR. WINN-DEEN: "Decision-making processes and coverage/reimbursement decisions."

DR. FITZGERALD: "Decision-making processes and"?

DR. STRAUBE: "And policies."

DR. FITZGERALD: "And policies," "coverage policies." That is what we were trying to get at. All right.

One of them has to go longer than all the rest, so hopefully this is it. Here we are. Recommendation No. 9, going once, going twice?

[No response.]

DR. FITZGERALD: And it is finally put to rest. There we go.

MS. AU: Kevin, before you go to No. 10, can I say something? It is not about No. 9. No. 9 is fine.

This seems to be the only place we are talking about reimbursement. Some of the other reimbursement issues we had brought up in our Reimbursement and Coverage Report. It just seems like we have to put some recommendation in there about some of the things that we mentioned in there about genetics expertise.

DR. FITZGERALD: It is referenced, certainly, in the report, that is correct. Yes, it is referenced in the earlier report on coverage.

MS. AU: I think that in our reports that have been after the Coverage and Reimbursement Report, like the Large Population Study one, we actually referenced the report in the recommendation.

DR. FITZGERALD: So you are saying we could do what we did here before and

put a little footnote or something?

MS. AU: Not for Recommendation No. 9. I'm just saying as a separate recommendation. This is the only area where you talk about reimbursement. Later on you do talk about education and all that other stuff, but it doesn't talk about how you pay for some of those things to help with the understanding and education. So you are only going to talk about reimbursement in this one section.

DR. FITZGERALD: Let me get this right. You are not talking about Recommendation No. 9. You actually want Recommendation No. 9B. You are really going to hurt me.

Andrea.

DR. FERREIRA-GONZALEZ: We can say specifically that the issues that were covered in that report are still current and then the Secretary should go back and relook at that particular report.

DR. FITZGERALD: Yes. Do we want to make a recommendation to that extent?

DR. FERREIRA-GONZALEZ: That's it. We are saying that the issues dealt with in that report are still currently valid.

DR. FITZGERALD: What we are doing is this 9B right here. Come on, Sylvia. You started this.

DR. WILLIAMS: "The issues raised in the SACGHS Coverage and Reimbursement Report impact this report, and the Committee recommends that these issues be" --

DR. FITZGERALD: "Therefore, the Secretary should revisit" --

DR. WILLIAMS: "Review and apply and implement the recommendations from that report."

MS. AU: "To move forward on those recommendations." Act on those recommendations.

PARTICIPANT: Can I ask what the tenets of the other report were? We have to read all the reports if we come on the Committee.

DR. FERREIRA-GONZALEZ: Kevin, you might want to borrow from the report.

DR. FITZGERALD: No, we can't. We have to have the language.

DR. FERREIRA-GONZALEZ: "As the issues are identified in the coverage and reimbursement of genetic tests and services" -- right there.

[Pause.]

DR. FITZGERALD: There it is. Thank you, Andrea. Here we have Recommendation No. 9B, adding to our list of recommendations. "As the issues identified in the SACGHS Coverage and Reimbursement Report are still current, SACGHS urges HHS to act on the report's recommendations." Sylvia, is that okay?

MS. AU: Yes.

DR. FITZGERALD: It gets right to what you wanted. Excellent. Everybody is okay? Good? Wonderful.

Here we go. This is the Implementation Section. I am, again, not going to go through all these details. These are the issues we are going to try and address: education and guidance, IT, economic implications, ELSI, and coordination of HHS activities. So let's go right

to 10A, which is Slide 65, and that is on found on page 90 of your report.

The recommendation is that "HHS should assist state and other federal agencies and private sector organizations in the development, cataloguing, and dissemination of case studies and practice models relating to the use of pharmacogenomics technologies."

Comments, questions, confusion?

[No response.]

DR. FITZGERALD: Complete agreement. That we like. Everybody is good with this. Good. Next.

No. 10B. This is use of pharmacogenomics technologies in clinical practice and public health practice.

"HHS should assist professional organizations in their efforts to help their memberships achieve established competencies on the appropriate use of pharmacogenomics technologies. HHS also should encourage and facilitate collaborations between the organizations and the federal government around these activities."

DR. BILLINGS: Are there established competencies on pharmacogenomics activities?

DR. FITZGERALD: Are there established. "Should assist in their efforts to help achieve established." So you are saying do we have any now.

DR. BILLINGS: That is what I'm saying.

DR. FITZGERALD: My understanding was, if there are any, they are few and far between.

DR. BILLINGS: I don't think there are any, actually.

DR. FITZGERALD: Oh, I see what you are saying.

DR. FERREIRA-GONZALEZ: For example, the ASCO and CAP, that is a competency.

DR. BILLINGS: That is about as close as you can get to one, I think.

DR. FERREIRA-GONZALEZ: Yes, so we do have one.

[Laughter.]

DR. FERREIRA-GONZALEZ: Maybe we can encourage to have more.

DR. BILLINGS: If you take out "established" you get it, I think.

DR. FITZGERALD: So, take out "established." Good. Any other comments, questions, decisions about this one? Let's accept this as it is now. Going once, twice? No. Ellen.

DR. FOX: Change "memberships" to "members."

DR. FITZGERALD: "To help their members." Those are the kinds of suggestions we like: brief.

Here we go. Everybody is happy? We are happy? Yes. We are moving along to 10C. There are a lot of 10s, people. This one is on page 91.

This is pharmacogenomic technologies in clinical practice and public health practice. "As evidence of the clinical validity and clinical utility for a pharmacogenomics technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to professional organizations to facilitate the development of clinical practice guidelines."

Yes, Marc.

DR. WILLIAMS: I would just remove "professional organizations" because there are lots of groups that will develop clinical practice guidelines. They just need to be disseminated to facilitate the development of clinical practice guidelines. It may be AHRQ or others that would do that.

DR. FITZGERALD: Oh, I see. "Should be disseminated to facilitate." Good. Yes, Mara.

MS. ASPINALL: Are these reviews of the drug and this is post-market, so after the drug has been launched?

DR. FITZGERALD: "HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base." This is post-market, yes. Oh, it could be more?

DR. WILLIAMS: Well, if there is a good evidence base before somebody brings something to market, then there is no reason that that couldn't be done. I don't think it defines whether it is pre- or post-market.

DR. FITZGERALD: No, it doesn't limit it, but it is certainly post-market.

DR. WILLIAMS: What we are really talking about here is transparency of data and putting that on the public domain so that people can use it.

MS. ASPINALL: I'm trying to understand for a drug how this is different from what exists now or it is just that it is transparently available.

DR. FITZGERALD: Well, the transparency was certainly something we were attempting to achieve, that's for sure. I can't give you all the details on how that might differ from what exists now, not knowing it all, but Gurvaneet will do that.

[Laughter.]

DR. RANDHAWA: I will try. I think the intent here was focusing on the technology assessment and systematic evidence reviews, which are contingent on publicly available information, but also the fact that there aren't that many around. So even though there is a lot of information, its synthesis isn't that common, so that is what we were trying to encourage here.

MS. ASPINALL: So when you say "technology," you mean --

DR. RANDHAWA: It is broad.

MS. ASPINALL: -- microarrays, or do you mean a particular drug category? I'm just trying to figure out who is the person and what would they be doing this on.

DR. RANDHAWA: These are folks like the evidence-based practice centers, the Cochrane Collaboration, who will evaluate all different domains, whether utility, validity, anything of any drug, diagnostic device, anything that is relevant to clinical practice.

MS. ASPINALL: Those kind of organizations would be the people that you are talking about here that would have to do that, or that we are recommending to do that.

DR. RANDHAWA: Right.

MS. ASPINALL: Does that need to be clearer?

DR. TEUTSCH: No. This is already in place for other things, and this is just saying it should be applied to pharmacogenomics as well.

DR. FITZGERALD: Anyone else? Paul.

MR. MILLER: A wordsmithing thing. It may not have any meaning. But I just

noticed that as we go through the 10s, 10A, -B, -C, and -D, we are using the words, "assist," "support," and "facilitate," in each of them. Do they mean the same thing? Are they asking HHS to do the same thing in each of those contexts, or do they mean different things? If so, should you use the same word? It is just sort of a general question.

DR. FITZGERALD: So, "assist," got it. "Should facilitate," "should support."

MR. MILLER: One may have fiscal or resource implications. Maybe they all do. I'm just not sure.

DR. FITZGERALD: Yes. I'm just trying to see if I'm picking up any differences. I don't think so.

DR. WILLIAMS: I don't think there is anything in the text of the document that would support the fact that we had specific intent with any of those verbs.

DR. FITZGERALD: No, I don't think so.

MR. MILLER: It may be a distinction without difference. I was just asking.

DR. FITZGERALD: Right. No, I don't think so.

MR. MILLER: Somebody just pulled out the thesaurus, I think.

DR. FITZGERALD: We didn't want to be boring.

PARTICIPANT: At Recommendation No. 10 I think it is a little late.

[Laughter.]

DR. FITZGERALD: We never said we achieve what we want, that's for sure. Brevity we have not achieved.

No. 10C is where we are now. "As evidence of clinical validity and clinical utility for pharmacogenomics technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to facilitate the development of clinical practice guidelines."

People are happy with that? Looking around, I don't see any great suffering. We will say 10C is good and move on to 10D.

This is on the use of pharmacogenomic technologies again in clinical practice and public health care practice. "HHS should facilitate the development of evidence-based clinical practice guidelines and dosing guidelines by supporting consensus-building efforts among guideline developers. These consensus-building efforts should include development of standards that define the minimum levels of evidence required to support guideline decisions. These standards should take into account the clinical contexts (e.g., prevention, diagnosis, treatment) in which the pharmacogenomics test may be offered. Consensus-building efforts also should include standardization of guideline development methods."

I think most of the Committee has passed into unconsciousness, which is a good thing. This is what we have been working for.

[Laughter.]

DR. FITZGERALD: How are we? We are looking good. Gurvaneet.

DR. RANDHAWA: I think this wording is fine. I have nothing to add to this.

DR. FITZGERALD: Good. Thank you.

DR. RANDHAWA: But I did want to bring back one point that Steve had mentioned earlier, which was the original intent of Recommendation No. 9 on reimbursement. Is this a place where we can think about adding clinical utility information and how it informs

coverage decisions or is that recommendation not being considered?

DR. FITZGERALD: In 9B, since we have dragged in the entire previous report, I think --

DR. RANDHAWA: I don't know that that had the clinical utility and incremental benefit in there.

DR. FITZGERALD: I would have to look. Yes, Scott.

LT. COL. McLEAN: By reference to 10C, the clinical utility is right there. It is folded in because of the adjunctive recommendation.

DR. WILLIAMS: In some sense it is a symptom in search of a disease. If there really is demonstrated utility and incremental effectiveness, only idiots are not going to adopt that, or if there is specific contract language that prevents them from doing anything genetic, which exists. I don't know that we necessarily need to point that out. If the evidence is really compelling that this works, people will try and facilitate that happening.

DR. FITZGERALD: Thank you. Sylvia.

MS. AU: Can we get rid of the last sentence by making the first sentence "HHS should facilitate the standardized development of evidence-based," blah, blah, blah?

DR. FITZGERALD: Wait a minute now. "Should facilitate the standardized development of evidence-based."

MS. AU: "Clinical practice guidelines."

DR. FITZGERALD: What you are trying to catch is the standardization of guideline development methods in the first sentence?

MS. AU: Yes.

DR. FITZGERALD: Marc.

DR. WILLIAMS: I'm not sure it is necessary because there is already a standardized process established with Guidelines.gov. I don't think we are talking about any sort of a repository.

DR. FITZGERALD: Get rid of that sentence. Brevity is good, right? How about the brevity of moving along to the next one? Everybody good on 10D?

[No response.]

DR. FITZGERALD: Let's go to 10E. This is another one of the recommendations that came directly from the public comments. "To inform the development of pharmacogenomic tests and dosing guidelines, HHS should fund clinical trials that provide evidence on whether pharmacogenomics information is clinically useful and, if so, how to use this information in addition to other relevant factors (e.g., gender and age of patient, other medications being taken)."

Joe.

DR. TELFAIR: I'm wondering if part of this has not already been covered in previous recommendations.

DR. FITZGERALD: There is a little overlap, but we are not as specific as what we have here saying HHS should fund clinical trials to provide evidence.

Yes, Gurvaneet.

DR. RANDHAWA: There are two issues here. I think one is, I'm not sure we can always get this information from trials. It may be clinical studies, some trials, some not trials.

DR. FITZGERALD: Clinical studies, okay.

DR. RANDHAWA: The other aspect is, to some extent we have discussed this in a more generic form in the other when we were trying to improve the evidence base per se. Dosing is a very specific aspect. That is only one part of pharmacogenomics. One can argue about the other part, which is targeting the drug or tailoring the drug and what drug to take. Are we focused only on the dosing?

DR. FITZGERALD: The reason dosing is in there is it was specifically mentioned as needing to be in there by the members of the taskforce, not just to leave it. They thought it needed to be emphasized. That was the reason it is there.

Yes, James.

DR. EVANS: A question. Do we really need that last clause? "If so, how to use this information, in addition to other relevant factors." What does that add to it, and is that necessary?

DR. FITZGERALD: After the "and if so," right? You want to possibly end it right after "pharmacogenomics information is clinically useful"?

DR. EVANS: Yes.

DR. FITZGERALD: So we are just saying we don't need to emphasize the fact that integrating it with other --

DR. EVANS: We are looking at whether PGx is clinically useful. I'm not sure why we need that last part.

DR. FITZGERALD: Joe.

DR. TELFAIR: I would concur because I think we have already covered this part. I would concur with him.

DR. FITZGERALD: Oh, okay. Get rid of that.

So right now, take a look at what we have. What we have is, "To inform the development of pharmacogenomics tests and dosing guidelines, HHS should fund clinical studies that provide evidence on whether pharmacogenomics information is clinically useful." Basically, we are pushing the studies.

Great. I'm looking around. Going once, going twice.

[No response.]

DR. FITZGERALD: Yes, indeed. We are on to 10F. Thank you.

No. 10F. "Professional organizations are encouraged to submit clinical practice guidelines that they develop for pharmacogenomics testing to AHRQ's National Guideline Clearinghouse to facilitate dissemination and encourage their implementation and use."

Actually, I suppose we could phrase this a little differently and say "The Secretary should encourage professional organizations to submit."

DR. WILLIAMS: Again, I would just raise the issue with are we trying to be very specific about professional society organizations. There are healthcare delivery systems that also develop guidelines. I would want it to be a little bit more generic.

DR. FITZGERALD: So, "professional organizations and"?

DR. WILLIAMS: Or just say, "The Secretary should encourage organizations to submit."

DR. FITZGERALD: Good. Am I missing somebody? Okay. Great. Up there we have now, "The Secretary should encourage organizations to submit clinical practice

guidelines that they develop for pharmacogenomics testing to AHRQ's National Guideline Clearinghouse to facilitate dissemination and encourage their implementation and use."

Everybody seems happy with that. Wonderful. On to 10G. This is on page 94 of your report, still on clinical practice and public health practice.

"FDA and drug manufacturers should focus more attention on ensuring that all relevant pharmacogenomics information is included in drug labels in a timely manner. When a pharmacogenomics test is mentioned in a drug label, information should be included about the test's analytical validity, clinical validity, clinical utility, dosing, adverse events, or drug selection for clinicians to use when making treatment decisions based on pharmacogenomics test results. FDA should provide guidance on the standards of evidence that must be met for pharmacogenomics information to be included in the label."

This is our labeling recommendation. People seem to be happy with that. Good. Oh. Paul.

DR. BILLINGS: Was there a discussion about different parts of the label? That is, there is real estate on the FDA labels, and the question is I wonder whether the group thought about what part of the label we are talking about here.

DR. FITZGERALD: We did not. We thought it best to leave to FDA to decide that, not that we would make a specific recommendation to that content. Yes, Mara.

MS. ASPINALL: A related question. If a test is a laboratory-developed test and the FDA does not review it, how is that thought about in the midst of putting it on the label? Would the FDA get it from CLIA? How would laboratory-developed tests fit into this recommendation?

DR. FITZGERALD: Oh, okay.

DR. WINN-DEEN: I think it depends on what the test is. Obviously, if it goes through the codevelopment process, then you can have labels pointing at labels.

Let's use your Warfarin example. In that label it said genetic factors are a part of the other list of factors you should consider in Warfarin dosing. They didn't really go into even the specifics of exactly which snips should be tested for.

So I think it depends on what the evidence base is and what the commercial availability of a specific test is how much information you can put on the drug label. I think we wanted to just leave a laundry list of things that could go in there, but they don't all necessarily have to go in there.

DR. FITZGERALD: I have Ellen and then Steve.

DR. FOX: Shouldn't "or" be "and/or"?

DR. FITZGERALD: Where is that? Oh, you mean "adverse events."

DR. FOX: There is a long list of things that should be --

DR. FITZGERALD: "And/or drug selections," is that the "or" you are talking about? Thank you. Steve.

DR. TEUTSCH: Again, we are making recommendations for manufacturers here. It maybe should just say that FDA should work with manufacturers, and then get rid of the next phrase, to ensure that all relevant PGx information appears in labels. It would just be simpler.

DR. FITZGERALD: Oh, I see. Okay. Wait a minute. Let's make sure we get that. Steve, take a look.

DR. TEUTSCH: Yes.

DR. FITZGERALD: Paul.

MR. MILLER: I was just going to make the same point.

DR. FITZGERALD: Wow, we are getting on the same wavelength. That would be a really scary thing.

Excellent. Here is what we have. "FDA should work with manufacturers to ensure that all relevant pharmacogenomics information is included in drug labels in a timely manner. When a pharmacogenomics test is mentioned in a drug label, information should be included about the test's analytic validity, clinical validity, clinical utility, dosing, adverse events, and/or drug selection for clinicians to use when making treatment decisions based on pharmacogenomics test results. FDA should provide guidance on the standards of evidence that must be met for pharmacogenomics information to be included in the label."

Paul.

DR. BILLINGS: Can I just ask another point of clarification. Was it the subcommittee's view that the impact of the current labeling is an effective one?

DR. FITZGERALD: The impact of the current labeling?

DR. BILLINGS: I'm trying to put this in a politic way. Polite way, yes. Maybe "polite" is the right word, since I'm sitting next to Steve here.

[Laughter.]

DR. BILLINGS: But I'm just curious; is it working today?

DR. GUTMAN: Nobody believes anybody reads the labels.

[Laughter.]

DR. FITZGERALD: Yes, Steve.

DR. TEUTSCH: Just to be fair, FDA, number one, has improved the label, but beyond that, it is absolutely critical for what can actually be said about a drug. Although, I agree, docs won't sit there and read the label particularly, it is critical to what the companies can promote and educate about.

DR. FITZGERALD: Once, twice, three times?

[No response.]

DR. FITZGERALD: It is time to move on to 10H. We are picking up here.

DR. TUCKSON: It is 3 o'clock. You have the potential for a quick break. You can have a choice. You can just wander over and grab your coffee as the discussion continues to unfold, which is probably the best thing to do. You are always invited to use the facilities whenever you so desire.

[Laughter.]

DR. TUCKSON: I think we should just press on through. Just know that there is some stuff there. You just go get it quietly and don't trip over your neighbor.

DR. FITZGERALD: No. 10H. "NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label package insert information to people with Internet access. To ensure that all sectors of the public have access to this information, FDA and NIH should develop other ways to disseminate this information."

This was a specific information dissemination recommendation because, obviously, information is power. Everybody seems good with this. Good idea, like the wording. Great. Once, twice.

[No response.]

DR. FITZGERALD: And we are out of the 10s.

Recommendation 11A. There is light at the end of the tunnel, folks, and it is not a train. This is public education and engagement. "To inform the public about the availability, benefits, risks, and limitations of pharmacogenomics technologies" -- oh, I'm sorry. This been flipped.

MS. GOODWIN: If you look at 11B, that is the new 11A.

DR. FITZGERALD: Oh, I'm sorry. Gotcha.

MS. GOODWIN: 11A and 11B are flipped.

DR. FITZGERALD: That's right. If you look in your report, this is 11A. What was handed out to you as the slides was something we did earlier in the week that we changed. Yes?

MR. MILLER: Could I just make a quick wordsmithing? It is actually Sylvia, so she gets blamed. MS. AU: I haven't even read it yet.

MR. MILLER: No, this is on 10H.

DR. FITZGERALD: Oh, no, 10H is gone. No, go ahead.

MR. MILLER: It is a deletion. Basically, there is a redundancy. If you look at the first sentence, "NIH should continue expanding Internet-based project," blah, blah, blah, "information to people with Internet access." If it is Internet-based, it is people with Internet access. So I think you can drop that.

DR. FITZGERALD: The reason I think that is in there is the fact that in the next sentence we say people who do not have access to the Internet will also need to have this. So that was why it was there. It was a matter of emphasis.

MR. MILLER: A redundant matter of emphasis.

DR. FITZGERALD: Yes, we were trying to emphasize it over and over.

[Laughter.]

DR. TUCKSON: Do not let Sylvia lead you astray again.

MR. MILLER: I'm moving next to Paul.

[Laughter.]

DR. FITZGERALD: Now, 11A. Look at 11B, which is Slide 74 in your handout, but it is 11A in your report. This is also at page 96. We are all on the same page, or look up on the screen.

"To inform the public about the availability, benefits, risks, and limitations of pharmacogenomic technologies, HHS should ensure that credible educational resources are widely available through federal websites and other appropriate media."

Again, here the idea is to get the information out to the people and not only through Internet access but also through other means for people who do not have Internet or do not use it well.

Great. Everybody is happy with this? So am I. No, Joseph isn't.

DR. TELFAIR: I'm actually fine. There is just one tweaking of it. I'm not quite sure what the "credible" means when you talk about education material. A better way to talk about it is simple, plain language. Terms like "plain language."

DR. FITZGERALD: Oh, I see what you are saying. You are getting at more than "credible." It all has to be acceptable as far as --

DR. TELFAIR: Acceptable, right. Yes. It needs to be acceptable.

DR. FITZGERALD: What is the term for that? Sylvia, what is the term for that? Accessible?

DR. TELFAIR: Right, yes.

DR. FITZGERALD: There is a genetic counseling term that we use all the time.

PARTICIPANT: Appropriate.

DR. TELFAIR: I was trying to avoid the word "appropriate."

PARTICIPANT: It is already in there.

DR. TELFAIR: It is in there, right. That is the term that is used, is "appropriate."

DR. WILLIAMS: But HHS has standards for all of their educational materials.

DR. FITZGERALD: Thank you. So that is all part of HHS. They don't put anything on the website before it goes through those people who make it. Is that good enough? The fact that they do it already is okay?

DR. TELFAIR: Well, everybody does. If they do it already and this is going to HHS without going to the lay public, then no problem. But if it was going to the lay public, then I would have a problem.

DR. FITZGERALD: Sylvia.

MS. AU: How does the Secretary ensure that only appropriate media disseminate the information?

DR. FITZGERALD: No, no, no. Not "only." "Other appropriate media." In other words, a lot of people don't have Internet access or aren't Internet savvy, so there will be other ways to disseminate the information other than something through the website.

MS. AU: "Other media." I have to help Marc with his mantra.

DR. FITZGERALD: You want to get rid of "appropriate." Just get rid of "appropriate."

[Laughter.]

DR. FITZGERALD: "To inform the public about the availability, benefits, risks, and limitations of pharmacogenomic technologies, HHS should ensure that credible educational resources are widely available through federal websites and other media."

Thank you. Marvelous. 11B. For this one, Martin?

MR. DANNENFELSER: Should we say anything like "government websites," which could take in other states and so on? We don't have control over that, I guess, right?

DR. FITZGERALD: That is "other media." All right. Good. All right. No. 11B, page 96.

"HHS should use existing public consultation mechanisms to engage the public in a constructive dialogue regarding the potential benefits, risks, and limitations of pharmacogenomics technologies. This dialogue should include an assessment of their perceptions of and receptiveness to pharmacogenomics and their willingness to participate in clinical research studies involving these technologies."

We need to look at how we spelled "dialogue" throughout the whole report, but it is either with a U-E or not, one way or the other. There is another one up there.

Yes, Joe. Joe and then Paul.

DR. TELFAIR: I just have a question on some of the thinking. Why only clinical research studies involvement? There are other elements of engagement and dialogue that you

want related to utilization and access. So I would say "research studies access and utilization related to these technologies," something to that effect.

DR. FITZGERALD: "In their willingness to participate in."

DR. TELFAIR: "In," yes, "clinical trials."

DR. FITZGERALD: "In research studies."

DR. TELFAIR: "Research studies."

DR. FITZGERALD: "And"?

DR. TELFAIR: "And providing information on facilitation of access and utilization"? No?

DR. FITZGERALD: I have Paul and then I have Reed.

DR. BILLINGS: I was going to suggest that the first sentence is a little boggy to me. You might just say "HHS should use existing public consultation mechanisms to engage in a dialogue regarding the potential benefits, risks, and limitations," because public consultation will be public. We don't need two "publics."

DR. FITZGERALD: Right. "To engage in a dialogue regarding the potential." We are still working on yours, Joe.

I have Reed and then Steve.

DR. TUCKSON: Actually, he did mine. I wanted to get rid of that "widely." So "widely" was the last one. I wanted to get rid of that one in the last one. Then this one here in terms of "constructive."

We have to be careful. We put a lot of adjectives in here that make these things impossible, so let's try to be disciplined and get rid of unnecessary adjectives. So my point was, let's be disciplined when we finish all this and make sure that we are getting rid of unnecessary adjectives.

DR. FITZGERALD: We are going to have a paucity of adjectives. Steve.

DR. TEUTSCH: I was just going to try to talk about Joe's [remark.] I would probably have just concluded the end, "their willingness to use these technologies and participate in clinical research."

DR. FITZGERALD: Does that get it?

DR. TEUTSCH: I'm fine with that.

DR. FITZGERALD: "Their willingness to use these technologies and participate in research studies." Yes, Barbara.

DR. McGRATH: I guess this gets at the bigger question of asking them what questions and what will you do with the information. So if we just ask them if they are willing to do studies or willing to use the technologies, aren't we also asking them if they are not willing to use these things?

DR. FITZGERALD: Yes, exactly.

DR. McGRATH: Somehow the tone sounds like we want confirmatory information from the public.

DR. FITZGERALD: In the first sentence I think we were trying to get at that regarding the potential benefits, risks, and limitations of these technologies. So we get from them what they see are the risks and limitations, the harms and benefits, that kind of thing. Is that okay, Barbara?

DR. McGRATH: Yes.

DR. FITZGERALD: I don't see any hands, so let's look at what we have. "HHS should use existing public consultation mechanisms to dialogue on the potential benefits, risks, and limitations of pharmacogenomics technologies. This dialogue should include an assessment of their perceptions of and receptiveness to pharmacogenomics and their willingness to use these technologies and participate in," should we do "research studies"? Just "studies" is too broad. Just studies? Okay.

Everybody good with that language? We are good to go. Fantastic. On to No. 12. This is on page 105. In fact, this may be all of page 105. We got carried away. There are a lot of adjectives in here, but this is health information technology.

"The Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community and in consultation with DVA and DOD, should take steps to ensure the inclusion of clinically validated pharmacogenomics test results into patient records, along with decision support systems and tools to enhance appropriate test use and interpretation. Decision support systems and tools should include information about the availability of pharmacogenomic tests, patient test results, and relevant information for making treatment and dosing decisions.

"As the infrastructure develops, HHS should account for the needs of basic clinical and translational researchers to ensure that secure, consented clinical outcomes information is available to accelerate integration of pharmacogenomic breakthroughs into clinical practice.

"HHS should support efforts to establish standards for the development of electronic clinical decision support systems and tools. Pharmacogenomic test clinical practice guidelines should be developed in a manner that allows for their integration into such systems and tools."

Comprehensive, but we thought substantively useful. Yes.

DR. WILLIAMS: I'm not sure that this really captures what the groups are actually charged to do. While DVA and DOD may in fact be developing some guidelines to implement, the AHIC and ONC are basically developing platforms that will enable these to actually work within an electronic health record environment. They are not really dealing with content at all. It is just basically making sure that the clinical decision support engines will be able to access the relevant data to generate the algorithms that would arise from clinical use.

As I read that first paragraph, it really sounds like you are calling on those groups to work to develop content, and that is not their role.

DR. FITZGERALD: Our thought, if I remember correctly, was obviously you need both structure and content. One without the other is fairly useless. So I think we are looking for both. Do you have a way of refining that word-wise?

DR. FERREIRA-GONZALEZ: For example, in here we are saying "should take steps to ensure the inclusion of clinically validated PGx." I mean, are you asking them to determine what is a clinically validated PGx?

The idea is that they have to develop the infrastructure, and the coding and so forth needs to put this information in an electronic format. So I'm not sure we are really capturing what we wanted with this language.

DR. WILLIAMS: Basically, all of Recommendation 10 relates to developing the evidence and putting the evidence out in guidelines so that people can actually use it. This

recommendation, in my mind, since it is around the health information technology, has to ensure that the developments in HIT will be able to support inclusion of things like genomic information, which currently we don't have standards or ability to include in the vast majority of information systems. So that really needs to be the intent of this recommendation, in my mind.

DR. FITZGERALD: I have Reed and then Ellen.

DR. TUCKSON: It seems to me it is too much. I think it is redundant. For me, it just boils down to "The Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community and in consultation with DVA and DOD should take steps to advance the inclusion of pharmacogenomic test results into patient records, along with decision support systems and tools to enhance appropriate tests using interpretation," period. The rest of that paragraph is just redundant to me.

DR. FITZGERALD: So, "decision" take out.

DR. TUCKSON: All that goes. Then the second paragraph. Again, I'm not sure it says anything more. Once you have said it up front, this doesn't add any more to it.

DR. FITZGERALD: You would take out that paragraph, then?

DR. TUCKSON: Take it out, too.

DR. FITZGERALD: Take it out.

DR. TUCKSON: Then this last part about "HHS should support efforts to establish standards for the development of electronic clinical decision," that is built into what they are doing. So I would, again, take that out. They are already trying to, through the AHIC process, develop electronic decision support systems.

So "PGx test clinical practice guidelines should be developed in a manner," that is a double of the recommendation earlier. I don't think you need it there. So I only come up with the first two sentences.

DR. FITZGERALD: Yes, Ellen.

DR. FOX: I'm confused as to what this is asking the VA. All of our records are electronic. If you do a genetic test, it will be included in the electronic record today. So if the issue is developing uniform genomic data standards, then that is covered under 6C, where VA is asked to create uniform genomic data standards.

So I'm not clear on what it is that VA is being asked to do. I don't know what it means "to include clinically validated pharmacogenomics test results into patient records." I don't know what that means.

DR. FITZGERALD: Before I answer that, I have Gurvaneet, Scott, Jim, Marc. Gurvaneet.

DR. RANDHAWA: I agree with Reed's point. We should at least clarify the process and the structure first, which is what AHIC is doing. But also, I think what is lacking here is the content, not only developing some content as to what exactly the decision support should look like for what tests but also learning from it. If you look at decision support systems in the past, for example the ones created for potential drug interactions, our track record of how well they are used in decision-making isn't all that great.

So apart from creating the content, the pilot study also needs to figure out what is the best way of making sure it actually gets used in practice in a useful manner, which would require some pilot studies to be done by other HHS agencies, maybe beyond just AHIC.

DR. FITZGERALD: What would you add to the recommendation?

DR. FITZGERALD: What is lacking in the recommendation right now is there is no mention of any component of HHS funding some pilot studies to actually look at the issues about how to integrate tests into clinical practice. What are the best means of improving decision-making in that context.

DR. FITZGERALD: Going back to Ellen's point, you said there is already that information in the Department of Veterans Affairs' database; is that correct?

DR. RANDHAWA: Yes. Just to go back to another point, some studies have been done in terms of when there are critical drug interactions. There is an alert that comes up on the computer screen, do you really want to do this, [and they] override it. Well, different people have different means of overriding, and we don't even know exactly what is the decision in terms of override and how it actually supports decision-making.

So yes, there are tools available. How well they are being used in practice and how well they inform current utilization we don't really know a whole lot about.

DR. FITZGERALD: Who would pilot those studies?

DR. RANDHAWA: I guess any of the knowledge-creating agencies in HHS should be able to do that.

DR. FITZGERALD: HHS could. I just want to make sure we are capturing what you are recommending up here. I have "The Office of National Coordinator for Health Information Technology, through the activities of AHIC and in consultation with DVA and DOD," which we will get back to, "should take steps pilot studies."

DR. RANDHAWA: I think that is the structure that we were talking about which Marc had mentioned. I'm talking more about the content. The pilot studies would actually be, let's take these 10 pharmacogenomic tests and use them in the CPOEs, or whatever mechanisms we have, and find out how actually it has been used in practice and if it has actually helped the physicians, the pharmacists, or whoever is using it in their decision-making.

DR. FITZGERALD: Can you say that in six words?

DR. RANDHAWA: Not right now.

[Laughter.]

DR. FITZGERALD: Let's see if we can get it up there.

Now I have Jim, I believe, right? Did I miss somebody coming along here? No.

DR. EVANS: Mine is very brief. I like what Reed did in cutting that. I think that the reason that the VA and the DOD were put in there is [as] examples of [the use of] sophisticated electronic medical records, especially with regard to decision support systems. Obviously, these things will get into the medical record, but because of the gap that exists in practitioner knowledge, the decision support systems become very important.

DR. FITZGERALD: I think the consultation part was big, Ellen, with the DVA and the DOD. Consult with [you] because you already do a lot.

Marc.

DR. WILLIAMS: Just two points. One is about having something in the electronic medical record. I haven't seen the VA system, but my guess would be that the results are represented as images, not as coded data. An image won't work in decision support. You have to have coded data. The coded data elements are still part of the structural elements that are really necessary to be able to run decision support engines. Not all information in electronic medical records is equal.

So I'm basically arguing to say we need to keep the structural elements represented in this recommendation.

To Gurvaneet's point, I certainly don't disagree, but I wonder, as we look at the fact that this is a problem across all medicine -- and I always feel a bit embarrassed if we focus in on a pharmacogenomic test as opposed to trying to get everybody on their heart medications -- whether specifically recommending pilot studies around pharmacogenomic CPOE type of systems is the direction that we really want DHHS to go or whether there are bigger fish to fry that may in fact inform the utility.

I still struggle with the idea of where the best place is to really learn how these things work, whether it is really top-down or whether it is really something that has to be developed at each individual level.

If it really comes down to each individual level developing it, then it is really just a matter of being able to pull information from the sources to be able to run the engine that you want to run.

DR. FITZGERALD: Now, again, when we started this recommendation, we attempted to get both structure and content. That got cut down to a couple of sentences. Now we are trying to get structure and content again. Is there a way we can look at this and word it so we can get some of that in this single recommendation?

This is what we have so far. "The Office of the National Coordination for Health Information Technology, through the activities of AHIC and in consultation with DVA and DOD, should study how clinically validated pharmacogenomic test results are being incorporated into patient health records. HHS also should take steps to ensure the necessary infrastructure is in place to support the inclusion of pharmacogenomics in electronic health records and decision support systems and tools."

Is that enough? Ellen.

DR. FOX: I think the problem I'm having with it is the inclusion of the pharmacogenetics. It is unclear to me what that means. Maybe something like "support the use of decision support systems and tools relating to pharmacogenomics," or something like that. I don't think it is the data you are trying to get included.

DR. WILLIAMS: Well, it is, to some degree. I think maybe the word to use there is "to support the representation of pharmacogenomics data." Again, the data has to be in the system to do any of the other things, but it has to be in a system in the proper way. At least in the IT world, we talk about representing data or structured data elements, or whatever.

I don't know, but that is the concept that I think is really critically important in the second paragraph. We have to have the infrastructure to be able to put that data in there in a format that you can actually use it.

DR. FITZGERALD: Ellen.

DR. FOX: I'm personally not familiar with that word "representation," but I [like] the last word you used, the "infrastructure." Maybe you could use the infrastructure to support the decision support. But the word "representation," I'm just unclear on what that would mean.

DR. FITZGERALD: So, "HHS should take steps to ensure the necessary infrastructure is in place to support the representation of pharmacogenomics data in electronic health records and decision support systems and tools."

DR. WILLIAMS: So, "in electronic health records for use in."

DR. FITZGERALD: "For use in decision support systems and tools." Yes? Okay. That got Emily back on board. Scott.

LT. COL. McLEAN: Can I just ask for clarification of the meaning of the term "consultation"?

DR. FITZGERALD: Up in the first paragraph. It means that you consult with somebody. No. I think the target here is we were thinking again of getting the different groups. The Secretary is within HHS, so this is to go outside of HHS and consult with both you and the Veterans Administration on how you do it.

MS. GOODWIN: At least as you do it really well.

DR. FITZGERALD: Exactly.

MS. GOODWIN: You are ahead of the curve on this.

DR. FITZGERALD: This is HHS saying why don't we get together with the other groups that are ahead.

Gurvaneet.

DR. RANDHAWA: I will be happy to suggest some wording, but I agree with Marc's point. I want to get a sense from the Committee, first of all, is it something the Committee is going to support in terms of getting some studies about content? Now, whether it is pharmacogenomics or any other clinical decision support is a discussion we can have, and I'm sure we can learn clinical decision support from other areas and apply that to pharmacogenomics. But there isn't a whole lot going on in that area per se.

The second thing to keep in mind is, in the future when we get more funding for pharmacogenomic activities, it may be potentially viable to do this. But I want to get a sense if the Committee wants to go in that direction before I suggest any wording.

DR. FITZGERALD: Why don't we put your wording up and then the Committee will let you know whether or not they want to go in that direction. With what we have up there now, Gurvaneet, where would you -- oh, I'm sorry. Ellen, go ahead.

DR. FOX: Just one more comment. I just want to make sure that the Committee is not misled by the current state of affairs. I think VA has a very sophisticated electronic record system and very sophisticated decision support. I don't believe VA has any decision support relating to pharmacogenomics currently. This almost sounds as if we are going to consult with VA to learn how that is done or something. I just wanted to make sure the Committee was clear on that.

DR. FITZGERALD: We are just trying to get everybody talking to one another so you can learn from each other and whatever else is out there, rather than people being in silos.

MS. GOODWIN: Would you prefer that highlighted clause get moved down to the second paragraph and say, "HHS, in consultation with DVA and DOD"? Would that be a better place for it?

PARTICIPANT: Yes.

DR. FITZGERALD: Gurvaneet, how are you doing on your [wording]?

DR. RANDHAWA: I will give it a shot. I'm sure we will be modifying it as I speak. "HHS should fund pilot studies that develop clinical decision support systems of pharmacogenomic technologies." What I'm struggling with right now is "and facilitate or improve decision-making at the point of care." I would appreciate someone helping me with that language there.

DR. FITZGERALD: This is what we have so far.

DR. WILLIAMS: Let me take a shot at this.

DR. FITZGERALD: Go, Marc.

DR. WILLIAMS: "HHS should fund pilot studies that examine the impact on practice of decision support systems for pharmacogenomic technologies at the point of care to maximize evidence-based best practices."

What I think I hear Gurvaneet saying is that we know what to do and we know that there is clinical decision support. We have not been able to really figure out how to us clinical decision support to actually make the best practices go forward.

The example of the drug interaction is alert fatigue. Every time you order a drug, you get an alert and so you just tend to ignore them all. Does that capture it? I think that I can support that.

DR. FITZGERALD: I just want to recognize the fact that we started with three paragraphs, worked our way down to two sentences, and we are back to three paragraphs. So I'm going to invite Reed [to comment.]

DR. TUCKSON: I'm just a little bit concerned. We are trying to get to some consensus here, but we have spent an awful lot of the government's money today. I think we have to be real, real careful about how much stuff we are saying that they have to spend money on. It is just impossible when you add up the tab on this whole deal.

So if there is something that we can not recommend as new money but to be part of something else that is ongoing, I think we have to do that. But, keep a tab of this thing. We are out of control.

DR. FITZGERALD: We are still working on this. Don't worry. We will send you the bill, Reed.

Let's take a look as we go through. Here is what we have. "The Office of the National Coordinator for Health Information Technology, through the activities of the AHIC, should study how clinically validated pharmacogenomics test results are being incorporated into patient health records. HHS, in consultation with DVA and DOD, should also take steps to ensure the necessary infrastructure is in place to support the representation of PGx data in electronic health records for use in decision support systems and tools. HHS should fund pilot studies that examine the impact of clinical decision support systems for pharmacogenomic technologies on clinical practice at the point of care to maximize evidence-based best practices."

Marc.

DR. WILLIAMS: In the first paragraph we somehow went from electronic health records to patient health records. Those are two very different things in terms of a lexicon. We may want to include both, but I think the focus here is electronic health records.

DR. FITZGERALD: That was probably just moving words around. All right. Take a look because it has changed somewhat substantively. Has everybody now completely lost any focus or desire at this point?

[No response.]

DR. FITZGERALD: That is where we are. Reed?

DR. TUCKSON: I guess nobody went with me on eliminating anything.

DR. FITZGERALD: No, we are sending you the bill.

DR. STRAUBE: No, I'm going with Reed because there is no money, so it again

becomes a redundant recommendation. In fact, we are looking for ways to bring in the private sector. This particular Secretary is very eager to try to get things out of public-private partnerships, and in doing so, part of that requires other funding streams.

Perhaps you can work the last paragraph that HHS should explore establishing pilot studies but not bring up the funding issue.

DR. FITZGERALD: I see. "Should explore pilot studies." "Should explore" --

DR. WILLIAMS: "Development of."

DR. FITZGERALD: Or, "initiating"?

DR. WILLIAMS: "Explore development of pilot studies.

DR. FITZGERALD: "That examine the impact." All right. Gurvaneet.

DR. RANDHAWA: I agree with Reed. We don't have, especially AHRQ, a huge budget. But we are funding two pilot projects on clinical decision support. That was recently announced. So it wasn't pharmacogenomics, but at least there is some activity that is going on that AHRQ is funding.

DR. TUCKSON: That is what I'm saying. Be a little more practical about saying use the money to do this, to do this. That didn't come out right.

DR. FITZGERALD: Any other wordsmithing recommendations for this recommendation?

[No response.]

DR. FITZGERALD: We seem to be somewhat in agreement, at least in a nebulous kind of way. All right. So, once, twice, three times?

[No response.]

DR. FITZGERALD: We are on to 12B. We are getting there, folks. Slowly, but we are getting there.

Still on health information technology. "Until electronic health record systems become a universal feature of the healthcare system, HHS should identify other ways to make best clinical practices for pharmacogenomics more readily available to help providers as they are developed."

Yes, Joseph.

DR. TELFAIR: Just a few wording changes to make it a little more practical in terms of taking into account what was just recommended. If you can replace "other ways" with "systematic pathways."

DR. FITZGERALD: "Should identify systematic pathways"?

DR. TELFAIR: Right. "To make," instead of "best," "emerging."

DR. FITZGERALD: "To make emerging."

DR. TELFAIR: Right. That's all. Those are the changes.

DR. FITZGERALD: "Clinical practices."

DR. TELFAIR: Yes.

DR. FITZGERALD: Robinsue.

DR. FROHBOESE: I have a question about this recommendation. I just didn't understand it. Is this saying that HHS should make available general information about PGx or individual clinical information more readily available?

DR. FITZGERALD: I'm going to look now at our new version here. If we have new clinical practices for pharmacogenomics, "emerging clinical practices," and they can't

automatically be made universal because the health record system isn't universal, right?

DR. FROHBOESE: I'm just not sure [what] the relationship [is] between an individual's electronic health record and HHS making available best clinical practices.

DR. FITZGERALD: Emily.

DR. WINN-DEEN: I think the intent was that until you have the electronic health record and then the electronic decision support tools that draw from that record, and you need both of those, there needs to be some alternative way to get information to physicians about what the current best practice is. So maybe we need to wordsmith it, but I think that is where we were headed.

DR. FROHBOESE: Then I think it would be good to make that clear.

DR. FITZGERALD: Whoa. Wait. Suddenly everybody is awake. Wow, wonderful. I have Jim, Steve, Marc.

DR. EVANS: I feel in a way that 12B is wholly redundant. We have already discussed getting things out to professional societies, how to get them out to physicians, et cetera. I don't think we need 12B.

DR. FITZGERALD: There is a move afoot, obviously, to get rid of 12B. How many people here would be deeply disturbed and wounded if we do that?

[No response.]

DR. FITZGERALD: Wow. We are getting rid of a recommendation rather than adding one. What a concept. Is everybody good with getting rid of 12B? It looks good. Once, twice, yes. Gone.

Economic implications of pharmacogenomics. Here we go. "To ensure that investments in pharmacogenomics are well spent, HHS should gather data to assess the economic value of investments in pharmacogenomics relative to other health-related investments. This assessment should encompass the cost effectiveness of pharmacogenomics technologies and take into account their short- and long-term impacts on specific sectors in society as a whole."

Yes, Sylvia. You want 12B back. No.

MS. AU: No. Given my optimistic nature, it is difficult for me to say that this sounds very Pollyanna-ish. You are asking them to do an analysis that the federal government is going to analyze the money is well spent for this health-related initiative versus all the other millions of health-related initiatives that we have? It just sounds too Pollyanna-ish to me.

DR. FITZGERALD: Does Pollyanna want to respond? Go ahead, Steve.

DR. TEUTSCH: I like Pollyanna.

[Laughter.]

DR. TEUTSCH: I mean, it is true, but this is a fundamental problem of allocation of resources and somebody needs to pull it together. This is clearly not the only thing. We talked about doing this earlier on in terms of generating information. Someone needs to pull it together and make it available in a broader context. That's all.

It really doesn't say that there needs to be an elaborate investment here beyond pulling together the information that is available.

DR. FITZGERALD: I have Reed and then Barbara.

DR. TUCKSON: I'm going to continue to come back to just being the mean grinch at the party. There are too many recommendations. There is too much money, too many

things asked to do. This one is just absolutely, to me, unnecessary in the scheme of everything. If we can get rid of something, let's get rid of it. The list is too long.

DR. FITZGERALD: Barbara and then Ellen.

DR. McGRATH: I'm not sure about that one way or the other, but if we do decide to keep it, we came up with some language earlier on, on Slide 2 or 3, at about 6 o'clock this morning when we talked about it. I think we are encouraging HHS to encourage research in this area, right? So it is directed to NIH or CDC or other federal agencies. There was one early on that we used some language. Maybe it would fit better and make it more of a directive. To redistribute their funds or something like that. Do you remember that conversation?

DR. FITZGERALD: Yes.

DR. McGRATH: If that is what we are asking, we should maybe use consistent language.

DR. FITZGERALD: I think that was more focused on basic research concerns.

DR. McGRATH: Isn't that what you are asking, that there be research on the economics?

DR. FITZGERALD: No. 5A, Slide 42. If that is the one you are talking about, just to be sure.

DR. McGRATH: I just read this one as saying there needs to be more research on the economic issues, not just the scientific aspects. So it seems the same.

MS. GOODWIN: Is this the one that you are thinking of? It is talking about cost effectiveness and value of PGx.

DR. McGRATH: I guess. I thought we started off the sentence with "HHS" and something about NIH in there, "should redistribute funding." See, I didn't write them down. Maybe just never mind.

DR. FITZGERALD: So we have another move afoot here to get rid of a recommendation. Yes, Ellen.

DR. FOX: Although I generally agree with Reed that we need to be careful in the number of recommendations here, I want to advocate for keeping this one in. I think that this is an area where there is a potential to develop infinite numbers of tests at infinite cost, and this is a huge issue. This could actually take money away from other health expenditures in a big way. So I think just advocating for cost effectiveness analyses along with all the other research is important.

DR. FITZGERALD: Someone is disagreeing with Reed yet again. I don't understand it.

I have Barry and then I have Joe and then I have Scott.

DR. STRAUBE: I think I support getting rid of this, also, for reasons that I stated before. But also, when we are looking at economic value, if there is a business case to be made, it is often made by the people who will benefit from it. In the absence of the business case being there, it is often because there isn't a business case.

So this would be something that I would think that folks who were touting pharmacogenomics as being a cost-effective, positive thing, will likely have that information and be able to make it available.

The second thing, just as an aside to remind people, when we recommend to the Secretary that he do something, he can of course delegate that to any number of entities,

including back to this Committee.

DR. FITZGERALD: Oh, sure. We have been there.

[Laughter.]

DR. FITZGERALD: Joe.

DR. TELFAIR: I guess that last note is what I was going to look at, sort of a middle ground thing. I think that eliminating this is not unreasonable, but I would say that the intent of it can be encompassed with some of the recommendations made earlier about other studies.

It seems to me that [we should add it] to the list of other studies. Given that there is a choice to either accept it or not, I think the add-on is not only delegated but also to accept or not accept. [That] is my understanding of recommendations.

This is more of a compromise thing here. Eliminate the whole one but keep the fact that you really do need to have some kind of cost effectiveness study done, and add it to the list of other studies from earlier recommendations.

DR. FITZGERALD: Then you have to pick which one you want to put that in.

DR. TELFAIR: Then I would say we already covered it.

DR. FITZGERALD: You are happy with what was said earlier. I just want to be sure.

DR. TELFAIR: Yes.

DR. FITZGERALD: I have Scott now. Go ahead.

LT. COL. McLEAN: I just want to concur that I think it can be folded into some of the other recommendations. But from the way I read the Personalized Health Care Initiative, cost savings is a fundamental tenet. If it is not addressed intrinsically, there will be plenty of critics and members of the loyal opposition that will address it for the Secretary.

DR. FITZGERALD: Steve.

DR. TEUTSCH: I will only point out that this was basically to look in a broader context rather than what is in there earlier, which is specific studies of cost effectiveness and specific technologies which are not in any particular context.

DR. FITZGERALD: Joe, go ahead.

DR. TELFAIR: I understand what was just said, but I think that there is still the option to expand it beyond just that. Even though it is made a specific recommendation, there is still the option. Cost effectiveness studies, by their very nature, can either be very specific or also broad, and they cover areas that are relevant to the assessment itself.

So I would still argue to eliminate it but to highlight that it is encompassed in an earlier recommendation.

DR. FITZGERALD: There does seem to be a little clarification required here. When you look at 5B, 5B is under that general rubric of establishing an evidence base for pharmacogenomic technology. That is not exactly necessarily the same as this. It is also in the first section of the report, which is the basic research, translational, clinical section of the report.

Now, we could say that this research is part of that basic research for pharmacogenomic technology. I don't think most people would conceptualize it that way, but I think if we do do that, and of course the Committee can decide to do that, we would have to clarify in the larger report that that is indeed what we are doing. I'm not sure people would naturally fit with that.

So I would say that is an option that we can take. It seems right now we have the option of keeping this recommendation and reworking it however we wish, getting rid of the recommendation, or getting rid of the recommendation and then in an earlier recommendation mentioning this and then in the report explicating what exactly we mean by having that in one of the earlier recommendations.

DR. TELFAIR: Make clear it is another piece of the evidence.

DR. FITZGERALD: I think when people talk about the evidence, as we were talking about before, we were thinking more the biological evidence rather than the economic and financial. But we can make that clear. That is a possibility. All these things are possibilities.

What I need now is a sense of where people wish to go. Are we going to rework this? Let's just do it this way. People who are generally in favor of still trying to hang on to this recommendation and rework it in some way, indicate by standing up or raising your hand. If anybody wants to try and fight this one.

[Show of hands.]

DR. FITZGERALD: Three, okay. Four, Michael.

Let me think of it this way. How many people would like to move this idea to an earlier recommendation and then explicate it clearly in the text that that was what was done and this is part of the evidence of establishing pharmacogenomic technologies?

[Show of hands.]

DR. FITZGERALD: We have 10. That is a much larger group.

The third is just drop it. Reed, Martin. What did you do, slip him a twenty, Reed, to make him vote?

It looks like we are moving toward the compromise sort of thing, if one wants to look at it that way, of dropping this one where it is and mentioning the need to do this in an earlier way. So we will probably have to go back to 5B, if that looks like the best place to put it. What is A?

Everybody quickly look at 5A, which is Slide 42. We talk about "HHS should provide resources to identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness and value of pharmacogenomics." We could then have to explicate in probably the executive summary as well as the text what we mean by "value" in that it would include this.

People are happy? I see generally people are happy with that. Done. No. 13 is gone. No. 5A, "value," we will include that. Thank you.

No. 14, which is on page 113 of your report. This is ethical, legal, and social implications research.

"NIH, in collaboration with other agencies, should continue to encourage and fund research on the ethical, legal, and social implications of pharmacogenomics. This research should include studies of whether integration of pharmacogenomics into clinical and public health practice exacerbates health and healthcare disparities, limits access to or decreases the quality of health care, increases medical liability, or results in genetic discrimination."

This is building on what is already there. I have Michael.

DR. AMOS: Does this not say the same thing as the economic value? This is part of the value equation.

DR. FITZGERALD: Paul?

DR. BILLINGS: It struck me as a little peculiar that in the text it is talking about disparities that exist and are widening in our society and the recommendation is for NIH to study it. Is there no stronger commitment that we could make in this document to the reduction or the anticipation of disparities widening without more directed policy and action on the Secretary's part?

DR. FITZGERALD: I'm trying to get to both questions at the same time. One could, in a really broad conceptualization of value, pull in ethics and legal issues and all that sort of thing. But due to exactly what Paul was just mentioning, the significance of these issues, this was seen as important to highlight.

Now, in that highlighting, what can we get at. In looking at the literature and discussions of this sort of thing, as you may well know, there are arguments back and forth whether or not pharmacogenomics actually will reduce healthcare disparities or exacerbate them. That is something that is still ongoing. So the idea was that perhaps study is not enough. There was a sense of, also, a continual review of what is going on to make sure that it doesn't in fact create greater healthcare disparities. I'm not sure we captured that in here.

Paul, go ahead.

DR. BILLINGS: Could you say, "should continue to encourage and fund research to avoid adverse social, ethical, and legal implications of PGx, to include, or including, an exacerbation of healthcare disparities, limits of access, and genetic discrimination," period?

DR. FITZGERALD: I think the idea was definitely to avoid. Go ahead, Paul.

DR. WISE: I like that. This is still about research that is going to come on line in five or 10 years, more likely, with this kind of research. Is there nothing in the document that is going to say that the Secretary should help develop policies that will facilitate access to advances in pharmacogenetics?

In other words, we already know differentials in access are profound. We also know that that will affect who in fact utilizes these advances, as opposed to doing research about it, which I think is fine. But, is this the only place where disparity reduction is going to be addressed?

DR. FITZGERALD: As far as a specific recommendation, yes. But we could put it in, if you would like to suggest some language. We will hear from Marc.

DR. WILLIAMS: I think the one other recommendation that we have talked about that does address this, at least peripherally, is the idea that we do have federally funded health care provision, Medicare, Medicaid, SCHIP, where we are essentially giving direction to say we think there may be some problems in terms of how we could actually fund this which will have an impact on being able to actually provide the services.

If that can be studied in a relatively short turnaround time to direct policies relating to coverage and reimbursement, that would impact disparity. So there is one other thing that at least indirectly impacts what I think you are talking about.

DR. FITZGERALD: Paul, did you have that language that you wanted?

DR. BILLINGS: I changed it to slightly more active. "Should continue to encourage and fund research to avoid adverse social." We could actually add, "And the Secretary should develop policies based on the likelihood of that outcome," or something like that.

DR. FITZGERALD: Let's go back up here. "Encourage and fund research to avoid adverse ethical, legal, and social implications of pharmacogenomics"? Does that capture what you had?

DR. BILLINGS: Yes, yes.

DR. FITZGERALD: Then, "This research should include studies," and then in the end, "adverse ethical, legal, and social implications," right. Then, "HHS should develop policies."

MS. AU: Kevin, I think at the beginning it should be "The Secretary or HHS should direct its agencies to develop policies and support activities that would discourage health disparity surrounding PGx," something like that. "HHS should direct its agencies." Or, "The Secretary should direct its agencies," "the HHS agencies" -- I don't know how that works -- "to develop policies and support activities."

DR. FITZGERALD: Marc?

DR. WILLIAMS: Steve and I were just chatting. I guess maybe the thing we need to narrow down here is that the research doesn't need to be overall. We all know that there are tons of healthcare disparities. So in some sense, it is an exceptionalism argument. Is this going to be different than all the other disparities that are already out there.

Maybe what we need to say is, are there specific issues related to pharmacogenomics. That is what we need to study, the things that pharmacogenomics would specifically increase disparities over and above all the other disparities that we already have.

DR. FITZGERALD: Also, my sense is that we want to be more proactive in addressing the use of pharmacogenomics to reduce disparities currently, right?

DR. WILLIAMS: Yes.

DR. FITZGERALD: That is what we are trying to capture. Robinsue, yes.

DR. FROHBOESE: I have some language that might accomplish that. How about, "HHS activities should support integration of PGx into clinical and public health practices that reduce health and healthcare disparities, increase access to and quality of health care, decrease medical liability," although I'm not sure whether we really need to include medical liability, "and reduce or eliminate genetic discrimination."

DR. FITZGERALD: Hang on. It is going to take us a little while here to get all this.

DR. FOX: Rather than focusing on studies, focusing on the impact, which is just picking up on the comments of others.

MS. GOODWIN: I don't know if you can see it, but let me know if I'm typing what you said correctly.

DR. FITZGERALD: We have "HHS activities should support integration of pharmacogenomics into clinical and public health practices in ways that reduce health and healthcare disparities, increase access to" -- what happened to "health"? You cut something out. Put something back. "Increase access to and quality of health care, and reduce genetic discrimination."

Is that close, Robinsue?

DR. FROHBOESE: Yes.

DR. FITZGERALD: Now, comments? Paul.

MR. MILLER: I was just listening to it and I was just thinking, if this really

changes anything, adds anything new, or is a restatement of what, presumably, is already being done. To the extent that it isn't really directing HHS to do anything different, I wonder whether it is necessary or whether it can be folded in, or whether in fact there are political reasons why you want an ELSI recommendation. I just put those thoughts on the table.

DR. FITZGERALD: Yes, Robinsue.

DR. FROHBOESE: Paul, I think, just as we have the recommendation about privacy and confidentiality because it is such an important principle that underscores the basis of the Committee's recommendations, so too I think this [belongs here.]

MR. MILLER: I think that's fair and appropriate, but I just wonder, if we are going to have an ELSI recommendation, and I don't necessarily know what it should be, but whether there should be something that really is a little meatier, maybe goes a little further or says something a little different other than just supporting ELSI issues. I mean, let's spend some money.

[Laughter.]

DR. WILLIAMS: To me, that is actually a justification for including it, because there are specifically designated ELSI funds. What we are really talking about is reordering the priorities where the Secretary could say, I would like a certain amount of these ELSI funds to be designated around issues of pharmacogenomics specifically. So there may be a practical reason.

DR. FITZGERALD: Right. Jim and then Paul.

DR. EVANS: I just want to remind people that I think the genesis, or at least one of the starting points for this was, again, the idea that is out there among many that pharmacogenomics may be less problematic from an ELSI standpoint than many other aspects of genetics. Thus, I would be in favor, if we are going to keep an ELSI bullet, that we emphasize studying that. Is pharmacogenomics indeed less problematic than other genetic technologies, and something to the effect that is obviously of great importance to minimize problems that are found.

I just want to remind people that there is a specific pharmacogenomic ELSI question.

DR. FITZGERALD: Paul.

DR. WISE: This is an ELSI question which can be addressed in a well-worded research statement that I think would be helpful and appropriate. But, there is a broader context. Just like there was the focus on race and ethnicity, you have this new arena of technical innovation. At some point, is this Committee going to recommend that the Secretary facilitate access of these new advances to all people in need, period.

In other words, it is not a research question alone. There needs to be attention to this research question, but at some point the decision might have to be made whether the Committee is going to recommend that this is such an important arena of technical innovation and health care that this Committee states clearly and sharply that the HHS needs to facilitate access to these advances to all people in need.

DR. FITZGERALD: Anyone else? Paul, one follow-up question to that, and to everybody else, I suppose, too. What we had initially was focused more on the research. What we have now is the more active. Do we want to take what we have now and support it with further research? In other words, are we going to say, in order to do this, whatever research needs to be done in order to guide, or do we want to just stick with what we have here? That is, I

guess, my question. Paul and then Gurvaneet.

DR. WISE: I'm still a rookie on the club here, but my sense would be, if it is allowable, to go back to the original language for the research question. Except, maybe to expand beyond NIH because there are other agencies doing research in these areas. Maybe shorten it, as Paul was suggesting, or change it, because that was still focused on the research. I thought that was good language.

But then to have a second sentence area or even a second recommendation that merely states that "HHS should develop policies that facilitate access to pharmacogenetic interventions of value to all people in need."

DR. BILLINGS: I would only support Paul the Wise by saying that that statement should come first.

DR. FITZGERALD: Which we have right now.

DR. BILLINGS: Right. Then the research.

DR. FITZGERALD: The research can be in support of that.

DR. BILLINGS: Supportive of that.

DR. FITZGERALD: Gurvaneet.

DR. RANDHAWA: I was thinking about this because I think there is a bit of a disconnect here. I understand the sentiment. We don't want to do research for research's sake and keep on doing research. But I'm not sure we always know what policies will actually reduce or exacerbate disparities with intended or unintended consequences.

So I think the missing link is that, apart from research on the factors that can cause disparities, what we are lacking is research on interventions that have been shown to reduce disparities and then acting on that. I didn't quite see that being made in the recommendation.

DR. FITZGERALD: That is what we are going to try and do right now, I think, is try to also put in, perhaps second, the fact that more research is going to be required in order to perhaps develop the sort of activities that you were saying should be there to support the integration of pharmacogenomic technologies. So whatever research is necessary or useful in that regard we will also have in this language. Is that getting to the two Pauls' [comments]?

What we want to do is we want to wordsmith the second paragraph to fit better with the first, once Suzanne gets it all in there.

This is what we had originally in the research language. What we would like to do is, if we can, fix that to fit better with the first paragraph we have now, because we are going to keep that first. So, recommendations in that regard? How about we start off the second paragraph, "To this end," because that would refer to what we have in the beginning.

Yes, Paul.

DR. WISE: I apologize, but that first paragraph also seems like we are still talking about practice guidelines. In other words, integrating pharmacogenetics into clinical public health practices. We are really talking about broad access policies as well, in fact far more importantly. So it might be something like "should support policies that afford access to and then the integration of."

In other words, integration into -- I'm trying to follow as it is moving here -- clinical public health practice is not really what I was getting at. I think that is great. It is an important area. But, "should support policies that afford access to pharmacogenetic advances" or

"advances of value" or something. Just "advances" would be fine with me.

DR. FITZGERALD: Is "technologies" okay?

DR. WISE: Sure.

DR. FITZGERALD: "Pharmacogenomic technologies." Just that in and of itself. "Should support policies that afford access to pharmacogenomic technologies"?

DR. WISE: No, and then the other parts.

DR. FITZGERALD: "In ways that reduce health and healthcare disparities, increase access to and quality." We have "access" twice.

DR. WISE: Get the "access," too. Just go right to "quality of."

DR. FITZGERALD: "Increase quality of health care and prevent genetic discrimination." Is that what you had in mind?

DR. WISE: Yes.

DR. FITZGERALD: Paul? Also, Paul?

DR. BILLINGS: Yes.

DR. FITZGERALD: We have the Pauls happy. Now we are in good shape.

Then, "To this end, HHS should continue to encourage and fund research."

DR. WILLIAMS: Can you just say "that supports this goal"?

DR. FITZGERALD: Yes, fine. "Research," after that, "in support of this goal." Yes, Michael.

DR. AMOS: That would mean actually funding the development of better, faster, cheaper technologies because that is really the rate-limiting factor in getting it out to everyone, to have the technology cheap enough so that it can be accessible by everyone. That is a part of it.

So, do we say anywhere in here that HHS should fund the development of new technologies? Or is that appropriate? Because that is part of the equation.

DR. FITZGERALD: Emily, go ahead.

DR. WINN-DEEN: We had that in one of the earlier recommendations and I think we ended up taking out the specific reference to genotyping technologies. I think we left it more broad in the end.

DR. FITZGERALD: Right. But I think we had in those earlier ones about the value, which we are putting as a large concept now. So if, obviously, better, cheaper, faster would be valuable, then that would be the way that it would be pursued.

DR. WINN-DEEN: I'm not sure that you can make a broad statement that the cost of a test is always the gating factor.

DR. AMOS: That is not what I'm saying. I'm saying that within certain contexts, if it costs $100 to conduct a test, some people aren't going to have access to that, as opposed to $1 a test.

DR. WINN-DEEN: If a therapy costs $10,000 to administer, some people aren't going to have access to it. So I think it is both things.

DR. AMOS: That is part of the ELSI. That is part of the discrimination.

DR. WINN-DEEN: It is cost-effective medicine, basically. We were trying to talk about that in more general terms, I think.

DR. FITZGERALD: This is where we are. Let's read it. "HHS should support policies that afford access to pharmacogenomic technologies in ways that reduce health and

healthcare disparities, improve quality of health care, and prevent genetic discrimination. To this end, HHS should continue to encourage and fund research in support of this goal."

Did we capture it? Yes. Great. Fantastic. Moving on, we have two more recommendations to do. They are more related to structural issues. This is coordination of pharmacogenomics activities. No. 15A is that "An interdepartmental workgroup should be established to review these recommendations, assess whether and how to implement them, monitor HHS progress, and report back to SACGHS." This gets back to whatever we recommend could come back to bite us, as it often does. "The workgroup also could serve as a forum for discussion of other PGx activities."

Yes. Paul, Marc, and Joe.

DR. BILLINGS: I'm curious about whether this would have outside representation on it. You talk about "interdepartmental," which sounds like intergovernmental. Did you mean for that to be, or would you want, for instance, public-private partnership to be involved in this activity as well?

DR. FITZGERALD: Yes. Again, it is a recommendation to the Secretary of HHS, so I presume --

DR. BILLINGS: Are we talking about better coordination intergovernmentally or are we talking about something that has an outside component?

DR. FITZGERALD: Steve, go ahead.

DR. TEUTSCH: This is an intergovernmental thing.

DR. FITZGERALD: Fine. Marc and then I had Joe, right? Right. Marc.

DR. WILLIAMS: There is one concept I think we need to represent, and this actually gets at what Reed has been talking about. I think we have to have prioritization in here. Some of these recommendations are going to be easier to implement, some of them are going to be more important to implement.

DR. FITZGERALD: Right. Now, on that note, there is that possibility, but here is the logistical issue. If we have time and we decide to do it, we can certainly then give the Committee the opportunity to prioritize the recommendations.

DR. WILLIAMS: No, no, no. I'm saying in this recommendation, "An interdepartmental workgroup should be established to review recommendations, prioritize those recommendations, assess whether and how to implement them."

DR. FITZGERALD: Oh, I see. Okay. That's fine. That's good. That's even better than us doing it.

I have Joe and then Andrea. No? Just Joe.

DR. TELFAIR: I guess mine would be, given what we just said, a point of information. If I'm wrong on this, maybe Reed can correct me. But, if it is intergovernmental or interdepartmental, isn't that something we are going to do anyway, apart from this last piece of prioritization? Isn't that something that is going to happen anyway?

DR. FITZGERALD: No, that was not our understanding. That was not understanding, that it would happen anyway.

DR. TELFAIR: A point of information. If we understand that that is not going to happen anyway.

DR. FITZGERALD: No. Again, this was what we heard from our representatives of the various departments of HHS. At least some people there said they wanted

this as a recommendation to make sure that it happened. I'm representing that accurately, I do believe, but that was what we heard.

DR. FERREIRA-GONZALEZ: I don't think it costs any money.

[Laughter.]

DR. FITZGERALD: Just for your information. Thank you. Yes, Ellen.

DR. FOX: Do you mean "interdepartmental" or "intra"? Do you mean within HHS?

DR. FITZGERALD: Within HHS.

DR. FOX: Not other departments?

DR. FITZGERALD: Yes, yes. Other departments, yes. Right. This is government. Yes, Robinsue.

DR. FROHBOESE: I'm just trying to think of [about our] other reports. Have we been this prescriptive about actually forming a separate group to monitor, track, report back?

DR. FITZGERALD: My understanding is no. Has it happened before?

MS. CARR: Yes, sort of.

DR. FITZGERALD: This was in response to a request, again, from members of different agencies. They wanted this. Now we have it, I guess, in the LPS study, and that is probably also represented by their desires.

DR. FROHBOESE: I'm just thinking, in keeping with Reed's admonition about proliferation of workgroups and money, money, money, should this be the function of the ex officios of SACGHS?

MS. CARR: It may very well involve them. One would expect them to.

DR. FITZGERALD: I think they wanted, in fact, or some anyway, wanted that to be the case.

MS. CARR: I think it is maybe the Committee's recognition that this is a complex set of recommendations that would require a lot of thinking and deliberation on the part of HHS and the other agencies. I think it is the Committee's way of acknowledging that it is not just something that can just be taken up by the Secretary's Office perhaps by itself. So I think that is part of what you are getting at.

DR. FITZGERALD: Go ahead, Reed.

DR. TUCKSON: I will soften what I was going to say because the ex officios suggested it. It just seems to me that -- maybe because I'm from the private sector -- this is a priority. Figure out the best way to get it done and just get it done. I don't think you need to tell the Secretary how to run his business, that he has to create an interagency taskforce, which means somebody has to staff it. It gets very complex. Just get it done.

MS. CARR: Remember that we have a recommendation a little bit like this in the Oversight draft report, too, don't we?

DR. TUCKSON: Which is, again, reason for my point. All of a sudden, this Committee is suggesting that the Secretary establish four oversight committees. Come on. He can't do this. One committee will do it all.

MS. CARR: No, no. It could be the same.

DR. FITZGERALD: Go ahead and give them all the work. They have nothing else to do.

As far as the language of this recommendation, any suggestions? Ellen.

DR. FOX: If it is the ex officios that recommended this, I'm wondering if the ex officios in this room think this is a good idea. I'm not understanding how this would work or how it would relate to this Committee. I don't know if others share my view.

DR. FITZGERALD: Right. I can only try to represent what was said, but the idea was that there were members who thought it would be a useful recommendation because it would give them the impetus to pull together people from various silos.

DR. TUCKSON: Can I try language? "The Secretary is requested to take all necessary steps."

DR. FITZGERALD: Keep going.

DR. TUCKSON: I'm letting her type. "Is requested to take all necessary steps to establish and review and prioritize," whatever it was.

DR. FITZGERALD: So we have, "The Secretary is requested to take all necessary steps to review and prioritize these recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS. The workgroup also" -- no? Oh, you have to get rid of that, then.

This is going to be interesting because, if we accept this, it is going to be interesting to see what we think about the next recommendation. Yes, James.

DR. EVANS: Which brings me to my suggestion that we don't need that next recommendation.

DR. FITZGERALD: That is what I think we are probably going to get to. We just basically made this over again. Anyway, let's just see if everybody is happy with this as it is. It looks like we have a general -- no, yes? Good. All right.

No. 15A, which may be just No. 15 in a minute. We move now to No. 15, our last recommendation, which is that "HHS should assess the level and adequacy of resources being devoted to support the integration of pharmacogenomics into clinical and public health practice," we have already touched on that a little, "to be sure that gaps and opportunities identified in this report are addressed."

DR. BILLINGS: I would recommend this being removed since it is implied by the first one.

DR. FITZGERALD: I think I get a general sense of that. So as the person directing this discussion, I think we should just turn this into volumes and volumes. No.

[Laughter.]

DR. FITZGERALD: No. 15B is about to be gone. One, two?

[No response.]

DR. FITZGERALD: All right. No. 15B is out of here. We are just 15.

Now, before we move on to the next, Reed is going to interject.

DR. TUCKSON: First of all, that was extraordinary. Kevin is extraordinary. Let's applaud Kevin.

[Applause.]

DR. FITZGERALD: We are not done yet.

DR. TUCKSON: That is why you are getting your applause now. Take it while you can get it, my friend.

[Laughter.]

DR. TUCKSON: We have two things. We wanted to hear, before we vote,

public comment. As we invite to come up to the microphone Amy Miller of the Personalized Medicine Coalition, who has a public comment germane to our discussion, let me read you an Email that has come in.

"I have been listening with interest to today's webcast of the meeting on the draft pharmacogenomics report. I'm sorry I'm unable to attend in person. Please accept this Email as my public comment for the meeting.

"During the report recommendation overview, Dr. FitzGerald questioned whether sufficient evidence of a genuine pharmacogenetics-based effect in drug development has been demonstrated yet. In the area of HIV drug research, the answer is yes. Just this month, a peer-reviewed study was published describing ways to reduce CNS effects associated with administration of Sustiva based on genetic differences in the patient population.

"In my earlier written comments dated May 17th of '07, I also described the important genetic test component necessary in the prescribing of other HIV drugs. These examples illustrate the importance of this form of personalized medicine. They also demonstrate the importance of facilitating codevelopment of diagnostics and drug development for the benefit of patient care for serious life-threatening illnesses. I have copied the journal references below.

"Thank you. Robert Reinhard from San Francisco."

Anyway, a very reasoned and appropriate response. Robert, if you are still out there, thank you very much, and anyone else, for taking the time to inform the Committee's deliberations.

With that, do we have Amy?

DR. A. MILLER: Yes, I'm right here.

DR. TUCKSON: Amy, go for it.

DR. A. MILLER: Thank you. My name is Amy Miller and I am public policy director for the Personalized Medicine Coalition, a federation of over 100 organizations representing a broad spectrum of academic, industrial, patient, provider, and payer communities that seek to advance the understanding and adoption of personalized medicine concepts and products for the benefits of patients.

During the last SACGHS meeting, the PMC made public comments on the draft report that we have been discussing today and we also mentioned our work in developing business incentives for personalized medicine. We are pleased that many of our ideas were contained in the conversation that we had today, but I want to reiterate those incentives, which we believe will advance personalized medicine.

One, federal funds should be appropriated to expand and accelerate genetic and genomic research through research and development grants.

Two, FDA should put in place an accelerated approval process for personalized therapeutics and diagnostics developed together or developed separately but designed to work together. This reiterates the comment just made by the person watching over the Web.

Three, reimbursement practices governing new technologies have a profound impact on both patient access and also the incentives of industry to develop new technologies. Therefore, we urge you to suggest new policies that expand payer coverage and reimbursement of personalized medicine products and services focused on disease prevention and those that improve the efficiency and value of our healthcare system.

In that vein, PMC is developing ideas on reimbursement models that will promote

personalized medicine and pharmacogenomics. We expect to articulate these ideas through white papers, workgroups, and public meetings, and look forward to sharing the results of these efforts with you.

DR. TUCKSON: Hold on. Before you go, in Tab 6 of your books you will see a letter from Amy to the Committee as well that defines some of these things.

Amy, did you feel like -- I'm sorry to be overly familiar. I know Ms. Miller.

DR. A. MILLER: Doctor, but you can call me Amy.

DR. TUCKSON: I can call you Amy, MR. MILLER. I will call you MR. MILLER.

DR. A. MILLER: The recommendations that we have discussed this morning, and I know you have been attentive in the back there, do they speak to the issues that you have raised?

DR. A. MILLER: I think they speak quite well to the federal funds issue. I think it is appropriate the way you have instructed the Secretary to get it done and leave it open to the Secretary and director of NIH as to how to get that done.

DR. TUCKSON: Great. Thank you. Is there anybody on the Committee who would like to query MR. MILLER?

MS. ASPINALL: On the federal funds issue, I understand your answer. We had a lot of discussion on the reimbursement issue. Does it deal with the issues that you are talking about in terms of creatively thinking about new approaches?

DR. A. MILLER: One specific recommendation by this group is that prevention be covered by CMS, and I think that would go a long way to getting to the reimbursement issue. But I think it is a beginning and one step. I'm not sure the recommendations fully articulate the reimbursement issue, which is partly why PMC is going to be dedicating a considerable amount of time and effort to more fully articulate ways that reimbursement can drive the adoption of personalized medicine.

DR. TUCKSON: Thank you very much for your public comment and the letter that you wrote.

DR. A. MILLER: Thank you for your time.

DR. TUCKSON: Is there any other public comment that wants to be heard prior to our taking this vote?

[No response.]

DR. TUCKSON: Gurvaneet, you are not questioning.

Now, here is the deal. We are going to be okay in terms of time. We are going to quickly zip through the recommendations just so everybody can see them one more time. Be thinking about the totality of what we have done.

I would like for the members of the Committee who are ad hoc today and who cannot vote formally, which is all the new folk and some of the old folk. I have a list, don't I, somewhere of who can vote? Yes. Here are the people who can vote, just so you will know: Sylvia, Jim, Andrea, Kevin, Julio, Barbara, Joseph, Steve, this Tuckson fellow, and Marc. Those are the voting people.

We do want to make sure that all the rest of you [have input.] If you have any strong feelings, let us know through this last couple seconds here so that nobody feels like they are shut out and so you can feel like you are part of it even though you don't get to vote formally.

Kevin, why don't you zip us through just to look at them again one more time, and then we will get out of here by five. Nobody is going to mess us up with too much fooling around, but we will take some fooling around.

DR. FITZGERALD: Just to remind everyone, what you are going to see on the screen will be the only copy of our final versions right now. So nothing in your report, unless you wrote down all the changes yourself.

MS. GOODWIN: Just to add, I will be putting together a Word document with all of the final recommendations this evening, so you will have it tomorrow at your chairs.

DR. FITZGERALD: For those of you who have sight difficulties, I'm going to read each and every one as we go through quickly.

No. 1, "NIH should receive and put more resources into, 1) basic research on the biochemical pathways associated with drug metabolism and drug action, the genes and gene variations involved in these pathways, and the functions of those genes related to the safety and effectiveness of drug treatments and diagnostics; and 2) non-hypothesis-based approaches to the understanding of the relationship between genetic variation and individuals' responses to drugs." That was the first one.

Second, "As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful pharmacogenomics technologies and to assess their clinical validity and clinical utility. HHS agencies should facilitate the development of clinically useful pharmacogenomics technologies by investing more resources into all components of translational research, including the translation of basic research findings into clinical trials as well as the translation of clinical research findings into clinical and public health practice, insurance coverage, and policy."

No. 3A, "Where study results will be used to demonstrate safety and efficacy to support a pre-market review application, sponsors and researchers should be encouraged to consult with FDA and CMS early in the study design phases. This would help to ensure that these studies have adequate clinical study design (e.g., sufficient statistical power) and quality controls in place should the research later be submitted for regulatory review."

No. 3B, "As appropriate, NIH should consider making FDA's existing quality of evidence standards a component of their assessments of the scientific merits of grant and contract submissions."

No. 3C, "In situations where pharmacogenomic diagnostics are essential to clinical drug use, HHS should require its grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development and/or the pre-IDE review process."

No. 3D, "To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS should develop guidance and standards on how these samples and other participant data will be collected, stored, shared, and used." We will reference the earlier SACGHS Large Population Studies report.

No. 4A, "FDA should develop and implement guidance on the codevelopment of pharmacogenomics drugs and diagnostics. FDA's guidance should clarify the review process for codeveloped pharmacogenomics products. It also should promote collaboration between drug

and diagnostics developers."

No. 4B, "FDA's Office of Combination Products should coordinate FDA's review of pharmacogenomic tests and drugs to minimize delays in approvals of codeveloped pharmacogenomics products and to ensure timely access to such products."

No. 4C, "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics drugs and diagnostics, especially for smaller patient populations and/or markets."

No. 5A, "HHS should identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, cost effectiveness, and value of pharmacogenomics. Progress will require high-quality data resources; improved methodologies in the design, conduct, and analysis of observational studies; and empirical research on the evidence and standards necessary for making decisions for various purposes (e.g., coverage, clinical guidelines, performance metrics, value-driven health care) in different clinical contexts."

No. 5B, "HHS should initiate and facilitate collaborations between public (e.g., AHRQ, DVA, CDC, CMS, FDA, NIH, and NIST) and private entities (e.g., private health insurance plans, pharmacy benefits managers, healthcare facilities with electronic medical records, clinical research databases or genetic repositories) to advance the generation and sharing of knowledge on the analytic validity, clinical validity, clinical utility, cost effectiveness, and value of pharmacogenomics."

No. 5C, "HHS should encourage and facilitate studies on the clinical validity and clinical utility of pharmacogenomics and the dissemination of study findings, including negative findings, through publications, meetings, and information clearinghouses."

No. 5D, "HHS should provide mechanisms that promote interactions among basic translational, clinical, and outcomes researchers for the identification of endpoints and data elements to be measured. The goal of these interactions would be to maximize the value and utility of basic and translational research data for downstream assessment of the clinical validity and clinical utility of pharmacogenomics tests."

No. 6A, "HHS should encourage private sector entities, including academic institutions, to share proprietary data voluntarily to advance the development and codevelopment of pharmacogenomics products. Manufacturers should be encouraged to make their data publicly available to allow others to conduct research and publish such studies."

No. 6B, "HHS should work with the private sector to identify obstacles to data sharing and develop solutions to overcome these obstacles (for example, legal and data confidentiality assurances, intellectual property protections, funding of databases and health information technology)."

No. 6C, "HHS should work with other relevant departments (for example, DVA, DOD, and NIST) and the private sector to improve data sharing and interoperability among databases. Specifically, HHS should work with existing organizations to create uniform genomic data standards, explore ways to harmonize data analysis methodologies, and develop an infrastructure to enable data exchange. Data sharing and interoperability of research, regulatory, medical record, and claims databases will facilitate the study of the molecular pathogenesis of disease, the identification of targets for drug development, validation of pharmacogenomic technologies, assessment of health outcomes associated with the use of pharmacogenomic technologies, and determination of the cost effectiveness and economic impact of using these

technologies."

No. 6D, "FDA should identify, initiate, and facilitate research opportunities and public-private partnerships to encourage the development and codevelopment of PGx products (for example, the Critical Path Initiative and Biomarkers Consortium)."

No. 7, "Stronger data security measures will be needed as more pharmacogenomics researchers access patient data. HHS, through mechanisms such as AHIC's Confidentiality, Privacy, and Security Workgroup, should develop guidance on how to balance the protection, privacy, and confidentiality of personal data with access to these data for pharmacogenomics research."

No. 8A, "FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may be better biological predictors of individual differences in drug response than broad categories such as race, ethnicity, and gender."

No. 8B, "When drugs are shown to be more effective in certain racial and ethnic subpopulations, FDA should encourage manufacturers to conduct additional post-market studies to identify genetic and other biological, social, behavioral, and environmental markers that may underlie the differential drug effects."

No. 9A, "CMS should develop a guidance document detailing current Medicare, Medicaid, and SCHIP coverage and reimbursement of pharmacogenomics. CMS also should survey public and private health plans about their decision-making processes and coverage policies to help inform its future pharmacogenomics coverage and reimbursement decisions."

No. 9B, "As the issues identified in the SACGHS Coverage and Reimbursement Report are still current, SACGHS urges HHS to act on the report's recommendations."

No. 10A, "HHS should assist state and other federal agencies and private sector organizations in the development, cataloguing, and dissemination of case studies and practice models relating to the use of pharmacogenomics technologies."

No. 10B, "HHS should assist professional organizations in their efforts to help their members achieve competencies on the appropriate use of pharmacogenomic technologies. HHS should also encourage and facilitate collaborations between the organizations and the federal government around these activities."

No. 10C, "As evidence of clinical validity and clinical utility for pharmacogenomics technology accrues, HHS should support the conduct of systematic reviews and technology assessments to summarize the evidence base. These systematic reviews and technology assessments should be disseminated to facilitate the development of clinical practice guidelines."

No. 10D, "HHS should facilitate the development of evidence-based clinical practice guidelines and dosing guidelines by supporting consensus-building efforts among guideline developers. These consensus-building efforts should include development of standards that define the minimal level of evidence required to support guideline decisions. These standards should take into account the clinical context (for example, prevention, diagnosis, treatment) in which pharmacogenomics tests may be offered."

No. 10E, "To inform the development of pharmacogenomic tests and dosing guidelines, HHS should fund clinical studies that provide evidence on whether pharmacogenomics information is clinically useful."

No. 10F, "The Secretary should encourage organizations to submit clinical practice guidelines that they develop for pharmacogenomic testing to AHRQ's National Guideline Clearinghouse to facilitate dissemination and encourage their implementation and use."

No. 10G, "FDA should work with manufacturers to ensure that all relevant pharmacogenomics information is included in drug labels in a timely manner. When a pharmacogenomics test is mentioned in a drug label, information should be included about the test's analytic validity, clinical validity, clinical utility, dosing, adverse events, and/or drug selection for clinicians to use when making treatment decisions based on pharmacogenomic test results. FDA should provide guidance on the standards of evidence that must be met for pharmacogenomics information to be included in the label."

No. 10H, "NIH and FDA should continue expanding the Internet-based DailyMed project, which provides up-to-date, real-time prescription drug label package insert information to people with Internet access. To ensure that all sectors of the public have access to this information, FDA and NIH should develop other ways to disseminate this information."

No. 11A, "To inform the public about the availability, benefits, risks, and limitations of pharmacogenomics technologies, HHS should ensure that credible education resources are widely available through federal websites and other media."

No. 11B, "HHS should use existing public consultation mechanisms to dialogue on the potential benefits, risks, and limitations of pharmacogenomics technologies. This dialogue should include an assessment of their perceptions and of receptiveness to pharmacogenomics and their willingness to use these technologies and participate in studies."

Wait a minute. That doesn't sound [right.] Assessment of whose perceptions; the public? Okay.

"The Office of the National Coordinator for Health Information Technology, through the activities of the American Health Information Community, should study how clinically validated pharmacogenomic test results are being incorporated into electronic health records. HHS, in consultation with DVA and DOD, also should take steps to ensure the necessary infrastructure is in place to support the representation of pharmacogenomics data in electronic health records for use in decision support systems and tools. HHS should explore development of pilot studies that examine the impact of clinical decision support systems for pharmacogenomics technologies on clinical practice at the point of care to maximize evidence-based best practices."

There is no 12B and No. 13 is gone, so this will be No. 13 now, I presume.

"HHS should support policies that afford access to pharmacogenomic technologies in ways that reduce health and healthcare disparities, improve quality of health care, and prevent genetic discrimination. To this end, HHS should continue to encourage and fund research in support of this goal."

No. 15, "The Secretary is requested to take all necessary steps to review and prioritize these recommendations, assess whether and how to implement them, monitor HHS's progress, and report back to SACGHS."

DR. TUCKSON: A quick scorecard of what we are saying, and this is just giving some broad categories. You have two categories where you are saying spend outright bucks. There were two outright expenditures.

You have 24 recommendations that said either develop, facilitate, engage, coordinate, encourage, urge. So you did a lot of developing, facilitating, engaging, coordinating, urging, and considering.

You have three where you require or ensure that the Secretary do something, and you have five where you said identify and address or study something.

So again, that is not a bad actual mix when you think about it. Two finances; 24 develop, facilitate, engage, coordinate, encourage, urge, and consider; three require and ensures; and five identify/address studies.

DR. FITZGERALD: Yes, Marc.

DR. WILLIAMS: I'm sorry. Could you go back to No. 9B for just a second? I think we may have missed a concept that would be kind of important. I think as opposed to "still current," I would say "are relevant to recommendations in this report." We don't have to have the "still."

MS. ASPINALL: Can I ask a question? It was an awkward moment before, but for us new people, if we haven't identified which report this is, can you highlight the key points of what that said? We are telling the Secretary to go back to it.

DR. WILLIAMS: There is a series of 10 or 12 recommendations that basically look at barriers to reimbursement and coverage and lays out, I think in a very reasonable way, what the issues are and how they might be able to be addressed.

Some of the issues relate to genetic testing, and so essentially I think what this recommendation is saying is that this needs to expand and include pharmacogenetic testing and that some of these recommendations have not as yet been acted on. So it is a reinforcement of previous recommendations.

There is, in fact, an ongoing dialogue that is going to be taking place in the next month to specifically address some of those issues and get a progress report, so this is not outside of the context of the work of the Committee.

DR. FITZGERALD: Mara, do you want more information or is that sufficient? I can read you what is in it.

MS. ASPINALL: I was trying to understand it, because my concern is on reimbursement. Without this we are not taking a stand. We are just saying explain what happens today. So I wanted to understand what stand this took.

DR. FITZGERALD: "Recommendations cover a range of topics, including evidence-based coverage decision-making, Medicare coverage of preventive services, the adequacy of current procedural terminology (CPT codes) for genetic tests and services, billing by non-physician genetic counseling providers, and genetics education of health providers." Those were the topics that were addressed.

Then, in July, CMS sent feedback back on these recommendations, and then a small group, led by Marc, has been reviewing the comments by CMS. There will be a meeting with Barry in December.

MS. ASPINALL: Let me just ask one specific question on the CPT code piece. Was the recommendation that it was adequate or it was not adequate?

DR. WILLIAMS: Heck no.

MS. ASPINALL: I'm with you, then. I got the list. I now know what it does, but I don't know if you went "thumbs up" or "thumbs down." That is what I'm trying to understand

because that is kind of important. I got it.

DR. TUCKSON: We are going to make sure that everybody is comfortable. Did we accept the change and the augmentation just now?

DR. FITZGERALD: Yes. Is everybody all right with the change that Marc just put in?

DR. TUCKSON: Are we good? All right. Now we are going to vote on this package. We are not going to go one-by-one. We are just going to vote on the package. No line-item vetoes.

I want to make sure, again, we are not rushing through this. So even the members who can't vote, I assume that we have kind of gotten a consensus here and that everybody is feeling comfortable about this very important report. So I'm looking around. Paul?

DR. BILLINGS: Reed, as a de novo, newbie, rookie, whatever you called me earlier, first of all, I want to at least express my gratitude. Being part of this discussion today was really quite an amazing tour de force by the Committee members.

There are a couple of issues that, again, may be buried in the deliberations of the Committee which, I guess for the record more than anything else, I would like to address.

It seems to me that what we have learned from the provision of pharmacogenomics so far -- for instance on the issue of point-of-care testing versus lab-based testing, or on the role of proteomic-based testing versus genotype-based testing, or on the question of whether pharmacogenetic tests should become a gate for access to certain drugs for that matter -- there is data already present in the healthcare system for these things.

The report is relatively silent on that. I wonder whether the report is going to suffer because of that. So I just raise those issues. Again, I mentioned it at the beginning and I raise it now.

DR. TUCKSON: I think it is very appropriate to raise it again. I know that Suzanne will ensure that the narrative, as she has already committed to do earlier, will reflect this very important though. So the narrative needs to remind all of us that we are not starting with a blank piece of paper here, that there is a history. I think that is a very important comment, and you might want to work with her on that.

I'm looking around the table.

[No response.]

DR. TUCKSON: So the formal people, for the record, whose hands will raise or not will be Sylvia, Jim, Andrea, Kevin, Julio, Barbara, Joseph, Steve, Tuckson, and Marc. With that, all in favor of the recommendations as summarized in the last iteration, please say "aye."

[There was a chorus of "ayes."]

DR. TUCKSON: All opposed?

[No response.]

DR. TUCKSON: All those abstaining?

[No response.]

DR. TUCKSON: So moved. You all have done a hard day's work today. Wait till we get to Andrea tomorrow.

I will let Kevin do whatever kudos he needs, but once again, Kevin, you have done just terrifically and just wonderfully.

DR. FITZGERALD: Thank you, thank you.

[Applause.]

DR. FITZGERALD: It is just my continual effort to live up to you, Reed, or "Red."

DR. TUCKSON: Suzanne as well.

DR. FITZGERALD: That's right. Before we do end this, I would like, again, to take an opportunity to thank some people. We did some of that at the beginning, but there were some people that we didn't have the time at the beginning to specify.

First of all, again, I would like to thank everybody on the taskforce. Obviously this is a group effort, and that is what makes it so rich and I think what makes it so substantive. Again, thank all of you. Thank in particular Suzanne.

[Applause.]

DR. FITZGERALD: Her fingers have lost several centimeters in length being crammed on a keyboard.

Then I would also like to thank Sandra Howard. Is Sandra here? And Theresa Lawrence. Thank you very much.

[Applause.]

DR. FITZGERALD: As I mentioned before, the Lewin Group, but they should get some specific recognition. Cliff Goodman, Christel Villarivera, Erin Karnes, Lindsey Wu, Charlene Chen, Laura Peterson, Eric Faulkner, and Amanda Thomas out there in the audience. Thank you again.

[Applause.]

DR. FITZGERALD: Finally, thank you to the public commentators. We really did listen to what you had to say and it was very important in our understanding of how to go ahead.

And always, thank you, Reed, for your leadership.

DR. TUCKSON: Thank you. Now, as we close off, Robert is still out there, by the way. He sent us another Email.

[Laughter.]

DR. TUCKSON: So Robert, who hung in there until the end.

Also, I want to thank our transcriber, who is working diligently over there despite the fact that we keep forgetting to push these buttons.

I also want to knowledge the translators who are working so hard over there to try to make all this make sense, as well as our colleague from Gallaudet, who has set through this. We are pleased that you have come to do this.

[Applause.]

DR. TUCKSON: Also, finally, we want to thank the folk who are manning the cameras to make sure that this gets on the Internet. You guys are terrific back there.

[Applause.]

DR. TUCKSON: With that, we go to dinner tonight.

I always thank Abby. I haven't gotten there yet. I'm telling you about dinner. They don't think I'm going to thank Abby.

Abby, if you can hear me out there. I know you can because you never come in here when we talk about you. Abby has us going to the Old Ebbit Grille. We are to meet, according to Abby's instructions, at 6:15 in the lobby of the J.W. Marriott and then it is just a

short walk.

Now, tomorrow, no fooling around. You know we are going to start at 8:30, so woe befall anyone who is late. Thanks, everybody, again.

[Whereupon, at 4:58 p.m., the meeting Recessed to reconvene the following day.]

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