Update on Efforts of the SACGHS Pharmacogenomics Task Force and Review of Draft Report
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DR. TUCKSON: Now to the meeting. As you know, we are in the process of developing a report to the Secretary on pharmacogenomics and the opportunities and challenges associated with its integration into health care and public health. At our last meeting in June, we discussed some preliminary straw man recommendations. Following that meeting, the Lewin Group prepared a draft report, and staff revised the initial recommendations based on the committee's input. The task force met in September to further develop the report and recommendations. Our colleague, Kevin FitzGerald, who has assumed the chairmanship of the task force following the great work and leadership of Emily Winn-Deen, will present the results of this work, and we will have an in-depth discussion of the issues identified in the report and the revised recommendations.

We're going to spend about four hours on this important topic. By the end of the session, we need to have reached consensus on whether the draft report is ready to be released for public comment or whether further work by the task force is needed. A copy of the draft report is in your Tab 4 of your briefing book.

So with that, again, you're going to listen to these things, you're going to go through it systematically, and at the end of the day you're going to make a choice, after four hours or less, about whether or not the report is ready to be released or whether it has to go back to the task force, and whether it's released for public comment or whether it comes back to the task force.

With that, Kevin.

DR. FITZGERALD: Really, I'm just a spokesperson for Suzanne.

Thank you, Reed. As you heard this morning, I will have the privilege of giving you an update on where we are with our report on pharmacogenomics, and I would like to ask your patience while I begin by giving you a little more background -- Reed has already given you some -- before we dive into the report. First of all, just to say much appreciation for the task force committee. People have worked very hard, given marvelous insight and input into this report, and as usual there are some names missing from that list of people to thank, because regardless of how many times I tell them to put their names on there, Suzanne and Sarah and Yvette and Amita refuse. So there you go, but we don't want to forget them and all the incredible work that they have done in getting to where we are today.

Why are we here? Well, again, as we just heard, the great impetus to pursue personalized medicine and how pharmacogenomics will be a part of this, especially in delivering the right drug at the right dosage to the right patient at the right time. There are a variety of drivers behind this impetus. We have broken these down into research and development, health care system, public interest and public policy, and this comes right out of the Secretary's Personalized Health Care Initiative, as we've heard, which is one of the major initiatives for the Secretary.

The reason behind this, again, is because pharmacogenomics has significant promise.

By the way, I'm sorry. Yes, you do all have these slides in front of you. It's the handout from today, and we are currently on number 5. So you don't have to twist your necks around and pretend to be owls or whatever. Just read off the paper.

But for our Internet audience out there who don't have the handouts, in addition to the many promises that pharmacogenomics offers as far as improved productivity, increased safety and more efficient use of drugs, there are obviously many challenges that must be addressed in order to get pharmacogenomics integrated into the clinical and public health care practice.

What's our role in all this? Again, as we've already indicated, identifying the opportunities and the challenges that are ahead of us, and advising the Secretary on how the federal government can help to advance the opportunities in this field and to address the challenges; in other words, to develop this report and these recommendations specifically for the Secretary.

A little history. As you heard, we had the informational sessions. Well, you haven't heard this yet. We had the informational sessions a year and a half ago, in June. Then there was the approval of a report outline a year ago in October, the compilation of the federal pharmacogenomics activities, which you can find in Appendix A. We will mention that again. They are extensive. I think it's important to be aware of what's going on because this will be part of the challenge of integration. Then development of the draft recommendations that we put forth in June. We took your feedback and your responses on those and tried to rework the report integrating those responses and trying to move ahead so we could develop a report and recommendations for the Secretary.

So following the June meeting, the staff revised the draft recommendations based on our discussion, and in spite of the guidance of the new task force chair we were able to move ahead. The Lewin Group, if you need to identify the Lewin Group, look for the people in the room who look the most harried and dependent on caffeine. That would be that group over there in the corner, because we really put them through their paces these past several months, and they did tremendously well. So they developed the draft report. We brought that to our meeting in September and worked that over and dragged the horse to the middle of the stream so that we could get them off the horse and put them on a high-speed speedboat and send them down the river. They took our recommendations from that time and put them in the draft report that you see before you today.

So what are we here to do today? As we've heard, we want to ensure that all the major opportunities and challenges associated with pharmacogenomics have been identified. We want to ensure that the draft recommendations address these high-priority issues, and we want to ensure that the draft recommendations are the appropriate solutions for addressing the issues. So as Reed mentioned, we want to reach consensus on whether or not the draft report and recommendations are ready for public review. Of course, the most important goal is not up there on the slide, but that is to keep Reed happy. So that is why we're going to work very efficiently through these few hours that we have to achieve our consensus on where we are.

We want to get to this point so that the next planned steps might be pursued, however we decide to go at them today. Those steps would be, of course, to revise the report and recommendations based upon today's input, and then the Lewin Group will go out and look for input from 15 federal and non-federal expert stakeholders on various pharmacogenomics issues. This is scheduled to be done this winter. Then, of course, we will seek general public comment, which would be sort of late winter and into the spring. We would love to finalize the report and recommendations next summer and to release the final report in fall 2007 so that we don't take too many days off the Secretary's 800, or as few as possible.

The way the report has been structured for today is that we took three overarching themes: research and development; who are the gatekeepers that are facilitating or inhibiting the

development of pharmacogenomics, appropriately or inappropriately; toward the implementation of pharmacogenomics to improve outcomes in clinical practice. Now, as far as the research and development piece, this involves, obviously, basic and translational research, clinical research, and also the infrastructure enabling research and development, and then the ELSI issues involved in research and development.

In this section, we had five recommendations which break down into 14 subparts, and we will go through those piece by piece to identify if we have covered the terrain well and have articulated what the recommendations should be.

We will then move on to the next section. Again, these are the gatekeepers, industry, FDA, CMS and other third-party payers, and clinical practice guideline developers. In this, there's one set of recommendations, Recommendation 6, that has three subparts. It may appear to be a smaller section, but it was a section that was identified by the task force as critical to pharmacogenomics moving forward and requiring our direct addressing of these groups.

Then finally we will look at the implementation of pharmacogenomics, and that will involve education and guidance, information technology, economic implications, again the ELSI issues, and coordination of all the HHS pharmacogenomics activities. As you can see, there are a variety of recommendations here, also with about 14 subparts.

So we'd like to walk through the three overarching sections one at a time, go through the issues that we've identified in each section to make sure we've hit the major ones, and we're not obviously going to be able to do everything, but we want to hit the big ones, then consider the recommendations we have drafted and consider if they're going to be adequate to the task of identifying the issues, and then finally, since no institution can do everything all at once, the thought was that perhaps we should attempt to identify what the recommendations of highest priority should be so that we might be able to give, if we want to -- this is not written in stone, but we thought it might be useful to give back to the Secretary some of the recommendations which we would consider to be particularly high priority.

In trying to pursue this, we went to the task force and asked them which recommendations they came up with that they considered to be high priority versus the low. It's a simple high/low kind of delineation, and the task force identified 12 high-priority recommendations of the 31 subparts, and we have identified those by the little bouncing star on the right.

Now, as we know, stars may appear to be permanent, but they are not. They evolve, too. So these stars are not set in the sky. We can move them around. We can remove them. We can place new stars somewhere. It's our chance to play God. We can do that with this report. So I invite you to not feel like these things are set in stone. What we want is your feedback that we can give to the public and get their feedback on what we have come up with.

Okay. So there's one thing that we learned in Jesuit education. It's repetition, repetition, repetition. That's how we learn. So again, why are we going to do this? The issues are does the report cover the major issues, either any issues that have not been but should be raised in the report, what issues are of the highest priority?

Recommendations. Do the recommendations as they are currently worded sufficiently address a high-priority issue? Are there any recommendations that have not been but should be included? Are there any recommendations that should be deleted because they are low priority, they will not have enough of an impact on the problem, or they are not implementable at this time?

Then the prioritization. To what extent will addressing this issue via this recommendation advance the goals of pharmacogenomics, and is the federal government in a position to act upon this issue or recommendation?

I think now that you've heard this several times, everything is pretty clear in our heads, so we can start to get into the first section, which is research and development. Again, this breaks down into the four subgroups that I have mentioned before, and we want to look at the issues at this time. We'll get to the recommendations after we have gone through the issues.

Here are the issues. Basic and translational research. We have identified issues that say that more basic research is needed to advance understanding of the biochemical pathways associated with drug metabolism and drug action; the genes involved in these pathways and genes related to the safety and effectiveness of drug treatments. In addition, more translational research is needed to apply this knowledge to the development of clinically useful pharmacogenomics technologies. Finally, translational research studies, if designed carefully, can themselves be a source of data for downstream studies of the clinical validity and clinical utility of pharmacogenomic tests. These are three issues that we have identified.

When one looks at the co-development of pharmacogenomics drugs and diagnostics, other issues arise: the possibility of resistance by industry to co-developed drugs and diagnostics. Why? Concern for market segmentation, uncertainty about FDA regulations of co-developed products, the requirement for new collaborations between drug and diagnostic industries, and coordination of development processes. This can result in expedited FDA approval, fewer label changes and greater likelihood for provider uptake.

What about the application of pharmacogenomics to abandoned drugs? Many drugs have been called "abandoned" because they have failed to detect a significant treatment effect in a broad enough population group. A post hoc analysis of clinical drug trial data for which genotype information is available can enable the rescue of abandoned drugs for use by smaller population of high responders. In this area again, it's going to be important to look at what the incentives are for pursuing identification of new indications for existing drugs, because these incentives are mixed. We have this little breakdown here. This is not in the report as structured here, but this is what we put together.

If you look at the patent status, for instance, you could see that an industry might have more incentive if the drug or device is still under patent, less incentive if it isn't. If the adverse drug reactions are severe, there might be more incentive to pursue this, less if they are mild. There's certainly more incentive to pursue this if there's no availability of alternate treatments. On the other hand, if there is, there would be less incentive to pursue this application.

When we get to the orphan category, we have other issues that we have to look at. There are differences in thresholds for drugs in diagnostics. Right now, the orphan drug threshold is it has to be less than or equal to 200,000, while the diagnostic threshold is less than or equal to 4,000. This could favor development of pharmacogenomic drugs, but not their accompanying diagnostics. So the question here is it is unclear whether the FDA would consider a pharmacogenomics-based drug and orphan product if it confers large benefit to an orphan-sized population but a modest benefit to a large population, and this could be seen similarly for a diagnostic.

Then when we're trying to put the two together, how does one balance these differences in the 200,000 and the 4,000?

Clinical validity and clinical utility. Most pharmacogenomics research has yet to be translated into clinical practice. Adoption will hinge on evidence of clinical validity and clinical utility, and yet little evidence of this validity and this utility currently exists.

As far as infrastructure is concerned, pharmacogenomics research could benefit from integration of research and clinical databases, repositories and records. However, there are issues in this integration because data collection storage, modeling and transfer within and among pharmacogenomics databases have a lot of challenges, in infrastructure and in support, because there's variation in data formats, EHRs are in early stages, and there are different funding streams, stakeholders, administrative protocols, and organizational cultures.

As far as the ELSI issues involved in research and development, we have the privacy and confidentiality concerns relating to research records. Data access and utility may be lost in exchange for gains in data protection. As things are structured now, it is often seen as a tradeoff. One has to balance the protections of privacy and confidentiality against access and utility. Does that have to be the case? Are there new and creative ways around this problem, or is this a balance that we're going to just have to strike?

Secondly, pharmacogenomic test results may reveal secondary information. What do we do if they do? There are discrepancies between human subjects research regulations, the Common Rule versus FDA regulations. Not requiring pharmacogenomics testing as a condition for drug treatment could increase drug company liability risk. How do we address those issues?

On a more social perspective, indeed pharmacogenomics promises to advance the development of personalized medicine by identifying individual differences in drug response. However, that very identification could continue to stratify subgroups, and stratify them along categories that are problematic such as race. The example currently in the literature and in the media is the BiDil application. Or you could associate molecular subgroups with race, and that could reinforce the idea or the concept of race as a biological construct, and that could limit the availability of pharmacogenomic-based drugs to certain subpopulations. How do we continue to deal with that issue?

So those are the issues that we raised for this section. What I'd like to do now is ask these three questions: Are these the major issues? Are there major issues that we have missed? If these are the major issues and these are good, are there some that aren't of high priority and that we don't need to include in here, and which ones are of the highest priority for the federal government to address? What I can do is take some time now to get your feedback before we launch -- remember, we're going to launch into the recommendations after this, and we can then see if our recommendations do indeed address the issues that we have raised.

So first of all, I'd like to ask if anybody has any responses or reactions to the issues as they have been laid out in the report. Cynthia?

MS. BERRY: I don't know if this rises to the level of a major issue, and Reed will probably know more about this than I, but I do know that there's been some discussion about comparative effectiveness and having AHRQ and HHS and other entities helped by comparing drugs against one another to do the research so that across-the-board payers and providers would have access to information about which drugs would work best. That, I think, is gaining some interest and momentum, and I'm just wondering if it should be addressed even if in just a small way in this report, because it sounds on its face incompatible with the notion of personalized medicine, but I

think there can be ways to reconcile the two, and I'm just wondering if maybe some passing reference to it at least would be worthwhile.

Reed, you might want to expand on it, because I don't know enough and I haven't been participating in that group. But I know that there are several sectors of the health care industry calling for this, and I think HHS is aware of it.

DR. TUCKSON: I don't know if I know a lot more than you. I mean, the key issue here, obviously, as you have underscored, is that people really do want to have information about whether this new thing, whatever the new thing is, does it work better than the old thing. If it does, is it more cost effective when you look at the total management of the condition, from diagnostics through the therapeutic implications, to the testing cost and implications, to the safety, to the convenience. So I think it is right down the middle of the plate, Cindy, because what this is ultimately saying for these new personalized pharmacogenomic products is how do these things fit into the overall health care landscape in terms of throwing out old stuff and replacing it with new stuff, or is this synergistic or additive or combinatorial or whatever. But if you don't have that information in a health care industry like this, with 48 million uninsured people who can't get at anything, it will be very difficult for the new thing to ever break through.

DR. ROLLINS: I also would like to comment on the initiation of some type of comparative analysis in terms of diagnostic tests. I know that CMS has commissioned AHRQ to look at various tests for genetic cancer disorders, and one of the things that we've also asked them to take a look at is the effectiveness in terms of not only effectiveness but also the accuracy of the test, looking at measures of accuracy, including such things as sensitivity, specificity, receiver-operator characteristics, as well as likelihood ratios. So in that instance, yes, there are comparative tests which might be applicable in terms of determining whether or not one particular test is more appropriate than another.

DR. FITZGERALD: Francis?

DR. COLLINS: One of the practical issues with implementing pharmacogenomics in the regular standard of care medicine is the need for rapid turnaround and results, and clearly many circumstances where one would like to adjust the plan about what drug to prescribe or what dose to prescribe are not well served if it takes a week or more for the test to be returned. So the prescriber can make that decision. In fact, I think this could be potentially quite a major issue.

Until such time as everybody has their entire genome already pre-sequenced and sitting in their medical record, where it simply becomes a matter of a computer search to get the genotype, we are going to be, I think, very much at the mercy of what kind of technologies provide the kind of point of care, rapid turnaround results.

I didn't specifically see that flag as a research and development priority, but clearly that could well turn out to be rate-limiting. If we have wonderful data showing, for instance, that in the presence of a particular, fairly acute medical illness a particular pharmacogenomic test would be valuable in terms of illuminating what drug to give and at what dose, but you can't get that result quickly enough to actually influence that decision, then people will continue doing what they've been doing all along. So this notion of coming up with a means of accelerating turnaround time for these kinds of genotyping experiences when it comes to pharmacogenomics it seems to me has probably not gotten as much attention as it should, because until now most genetic tests are done in central laboratories where samples are shipped, and if it takes a while for the results to

come back, in many instances that has not been so critical, but here it could be. So I just wanted to flag that as another potential research need.

DR. FITZGERALD: Thank you.

Andrea?

DR. FERREIRA-GONZALEZ: Yes, I just want to bring up another issue to the committee. I sit on one IRB panel within our institution. Our institution has four IRB panels that are looking at some of this review. One of the things that caught my attention going through our current draft report is that it's very important as we move forward for our translation and research and the clinical research that when testing is going to be done, to go back to the patient or to put patients in different categories because you have a certain genotype or you will act upon a specific result from the laboratory, that these tests need to be performed in a CLIA-certified laboratory. There's current regulation, because even research laboratories are under CLIA. If you're going to report back the results, I'm not sure if all the IRBs throughout the country are really aware of this issue.

So either through communications at the Office of Human Subjects Protection or some other venue, make all IRBs aware of this particular federal regulation.

DR. FITZGERALD: Scott?

DR. McLEAN: To follow on after Dr. Collins' point about the practical implications of how to get the tests done at the right time, there is the prospect of doing presymptomatic testing so that you have those results in hand at the time that you need them for an acute illness or for an acute need. The military has a little experience in the area of doing G6PD testing beforehand in case you need anti-malarials that may or may not cause problems, depending on what your test results are, and the same sort of approach to illness might be leveraged with certain presymptomatic testing for pharmacogenomic applications.

DR. FITZGERALD: Scott, would you see that short of falling under the same issue as Francis?

DR. McLEAN: Yes, in terms of practicality, but it does raise a lot of ethical questions when you go down that road, but it will come up. If you're in a practice and you want to prescribe a particular medication but you know that you're going to run into problems based on the genetic profile of your patient, then you can know ahead of time that you're going to need to select a particular drug with better benefits.

DR. FITZGERALD: Okay, great.

What I'd like to do is just get a sense of the committee, where we are on these things. Again, as I said, nobody can do everything. We can't put everything in the report and all that. So what I heard so far is we have three issues that we can certainly put in. Now, let's start with Cynthia, because she had the first one.

Could you restate it and state it as you see it specifically relevant to the research and development section? Because this is the section it will be going into rather than, say, the application section, which we'll get to later, but if you want to bring it up again, it might also be applicable there.

MS. BERRY: Well, that's why I wasn't sure. I had a couple of issues written down, and I was trying to categorize them, and I thought this could potentially be in either the research section or

perhaps coverage. I don't know how you'd characterize it. It certainly doesn't matter to me where we put it. I just know that it's out there, and maybe when we have someone from AHRQ, perhaps others could inform us a little bit better and we can bring it up at a later time.

DR. FITZGERALD: Okay. I'm just guessing that that one might go better in the third section. So we're going to hold that.

Francis, definitely looking in R&D, how would you specifically phrase that?

DR. COLLINS: The need for additional research in rapid turnaround cost-effective point of care genotyping for pharmacogenomics.

DR. FITZGERALD: Okay, great. Got it.

Andrea?

DR. FERREIRA-GONZALEZ: I think just a sentence or two, and I'm not sure how you dealt with this issue, where the Secretary could work with OHRP to remind IRBs throughout the country that they need to have CLIA-certified laboratories performing testing when results go back to the patients, either through putting patients in specific different arms or different dosages. Every time a result of this testing goes back to the patient, it needs to be from a CLIA-certified laboratory.

DR. FITZGERALD: Okay, we got that. I think what we may have to do is, when we get the report more fleshed out, we'll have a good idea where that could slide in.

DR. ROLLINS: In terms of adding on and coming up with specific wording, and whether or not you put it in this section or another section, it might be something like, "In addition to looking at the clinical utility and clinical validity of the test, measures also evaluating accuracy should also be taken into consideration."

DR. FITZGERALD: All right. Is that good with what Francis said in also incorporating --

DR. ROLLINS: I think so.

DR. FITZGERALD: Good. Great. Excellent.

Yes, go ahead, Debra.

DR. LEONARD: One of the areas of research that I've noted as I'm trying to implement pharmacogenomics in a health care system setting is cost effectiveness research. What is the cost effectiveness of spending the money to do a test on 100 percent of patients where you know 10 percent of them will have a variant, versus what is that saving you in adverse outcomes? This type of research is really needed to support the clinical implementation of pharmacogenetic testing.

DR. FITZGERALD: Currently, we have that in the third section of the report.

DR. LEONARD: So there are research parts in the third? That's what I'm not sure about, where it goes.

DR. FITZGERALD: What do you mean by "research"? Right. So there's certainly the identification of a need for that kind of information as one tries to apply what the basic science and translational data is going to be to the clinic. But if you think it's important to have a statement about that in the R&D section, that's --

DR. LEONARD: Well, there are public health faculty who would like to be doing this research but don't have the funding opportunities to support their efforts.

DR. FITZGERALD: Okay, that's good.

Michael?

DR. AMOS: In reading the report, there seem to be some assumptions that I want to make sure I understand. The assumptions are, as Dr. Rollins was saying, that the tests are accurate, and I want to make everybody understand that there are only a handful of clinical diagnostic tests that currently have standard reference materials available, out of the 1,500 or 2,000 tests that are done all the time.

The other part of this is that in order to make the dream a reality of pharmacogenomics, and to get to some of the basic pieces that you need here as far as gene expression for everyone, genetics for everyone, to really make this happen, the technology simply is just not there right now. In order, as Dr. Collins said, to have a gene sequence for everyone, it still costs about a million, roughly a million dollars per person. That has to get down to $1,000 or less.

The accuracy of the gene expression measurements, the clinical microarrays and things like that, NIST has a major program in trying to figure out how to make those tests work better. Just the signal transduction problem is a big issue.

So there is a great deal of hope in this, but the technologies just don't exist to really make that happen.

DR. FITZGERALD: Emily, go ahead.

DR. WINN-DEEN: I just wanted to address that comment. I think the technologies to do rapid genetic testing are coming along, and there's actually an RFP out from CDC right now to develop rapid point of care testing for avian influenza based on genetic analysis. I think what you'll see coming out of that RFP is funding for a number of different technology platforms which could then be leveraged across, because you're still doing genetic testing, whether you're doing human genetics or infectious disease genetics, into the pharmacogenetics area. So I think one of the things we should do is make sure we're closing the loop between those kinds of activities within CDC in an area which might be perceived as quite different from this and understand that that same technology platform that CDC is funding and helping to move forward in terms of getting to rapid point of care molecular testing can also be applied in pharmacogenetics. So it's sort of double bang for your buck.

DR. AMOS: Yes, there are a lot of those. I mean, DHS has got tons of money going into rapid genetic testing with bio-threat agents that could be leveraged against what you're doing as well. But the other part of this is integrating all that data into some form that can actually be used and studied and learned from to implement new biomarker discovery. Dr. Gutman will tell you that if you look at the FDA website, there have been no new protein biomarkers approved by the FDA

over the last 10 years. So the system for discovery is a bit broken right now, and I think you have an opportunity here to change that.

DR. FITZGERALD: The two of you, in the report as it stands now there are a couple of different places where we emphasize the need for -- I'll call it education or public access to information, and this could certainly be in there. We certainly want to discuss the hopes and the goals of pharmacogenomics, but also make it realistic and let people know where it is we stand now. So that I think is already in there. We can be more specific in that regard.

But I also gather there's the issue of the cooperation and the interaction of these different groups that are already involved in it. We also try to address that in the report in some places. We can, again, be more specific in the report as to the issues you raise.

But then there was a third thing I was hearing, and actually it may have been more specific. I think maybe, Emily, you were talking about it in particular, a step that needs to be taken that is very concrete. Could you just outline that again?

DR. WINN-DEEN: I think it was really a reiteration of Francis' point, that it's wonderful to discover biomarkers, to validate biomarkers, but if you can't deliver the results back to the patient in a timely way for a physician to take action, then you've missed the implementation part of it.

DR. FITZGERALD: So that falls under that. Okay, good. Thank you.

If it's all right, and we do want to keep moving, let's get on to the recommendations, because I think that's really where we're going to have the rubber meet the road here.

What we have now, again, we are looking at the wording of the recommendations. Do they sufficiently address what they are intended to address? Are we missing any? Are there some that are there that don't need to be there because they're not a high priority, because they won't have enough impact on the problem, or they're just not implementable at this time?

So how will these recommendations advance the goals of pharmacogenomics, and is the federal government in a position to act upon this recommendation? Here's our first one, Recommendation 1A. If you wish, in your executive summaries, starting on page 5, you have the entire recommendations spelled out. On some of the slides we've truncated it a little bit, obviously due to space limitations. So if you want to follow along, on page 5 of your executive summary you have the recommendations beginning. We'll start with the basic and translational research ones, and this is 1A, that the "NIH should invest more resources into basic research on the biochemical pathways associated with drug metabolism and drug action, the genes involved in these pathways, and gene functions related to the safety and effectiveness of drug treatments." I think that's exactly how we have it worded in the executive summary, so these two are the same.

Any comments on this particular recommendation? Debra?

DR. LEONARD: It's really the genes and gene variations, because we very often know the genes but we may not know the gene variations. So somehow the gene variability from person to person is key to this recommendation, I would think.

DR. FITZGERALD: Okay. So you would want to put in "the genes involved in these pathways and gene variability and function"? Or would you just --

DR. LEONARD: You could say "and gene variations and functions related to the safety and effectiveness."

DR. FITZGERALD: Great. Thank you.

Everybody else is comfortable? Great.

Next, 1B. "NIH should support more translational research focused on the development of clinically useful pharmacogenomic technologies." These are sort of maybe boilerplate in one sense, but these were things that certainly came out of the report.

Oh, there's more. I'm sorry. There is more there in the executive summary, if you want to look at that.

DR. AMOS: Is it appropriate to comment on the philosophy used to do these sorts of things? I mean, up to this point, a reductionist has been used, one protein and one gene at a time. There's some broader work being done, but up to this point I think some of these -- like I said, there have been no new biomarkers. So I think it may be important for us to comment on the philosophy used up to this point, because no new biomarkers in 10 years is pretty significant to me. Are we taking the right approach, or should we be taking a more systems approach, looking at the systems medicine or systems biology approach to some of these things? Because right now, things aren't moving as quickly as we'd hope.

DR. FITZGERALD: We can certainly raise that issue, and I think that's a good thing to bring up in the research and development section, to say this is how we've gotten where we are, and in that process this has raised the question that you raise, do we need to be more open than we are currently to a more systems approach. We can do that. Does that for you translate into a specific recommendation, or is it okay just to put that in the -- I mean, to be clear and to put that in the issue?

DR. AMOS: I'd open it up to the committee to discuss.

DR. FITZGERALD: Okay. Anybody?

Yes, Debra.

DR. LEONARD: I'm concerned about the statement that there haven't been any new biomarkers in 10 years, because I'm aware of new biomarkers being introduced into the clinical testing arena yearly. So I'm not sure where that statement is coming from.

DR. AMOS: If you look at the FDA website and look at the new PMAs in diagnostics, I'm talking about protein biomarkers. There have been some new genetic biomarkers approved.

DR. LEONARD: What about the triponin?

Francis, maybe you can comment as well. I don't want to be hanging out here on my own at the end of the limb.

DR. COLLINS: I'm a little confused by this discussion as well, because I think we're not talking about the whole universe of biomarkers here, we're talking about pharmacogenomics, and to the extent that we have identified promising but perhaps not fully clinically validated examples of

genetic variations that are associated with drug response -- I mean, take all of the P450 opportunities, all of the VKRC1s, all of the things that we know about things like TPMT, I would not say at all that we're in a circumstance where there hasn't been a lot of progress. I think what's missing is that next step of full-fledged clinical validity established in prospective trials. But I don't think we need a systems biology approach to identify the potential candidates to put into those trials. I think the main rate-limiting step now is the trials themselves.

DR. LONG: To follow up on that, maybe Recommendation 1A and 1C should come before 1B.

DR. FITZGERALD: You want 1C to come before 1B. Is that right?

DR. LONG: Or said another way, if 1B comes after you put 1A and 1C together, that's the next step, taking those who were involved in the basic discovery and linking those who are doing the trials, the studies of the people who are actually being treated with drugs, so that they can collect that information and draw the conclusions, take that next step, as was just said.

DR. FITZGERALD: Now, Rochelle, just a quick question. I think we broke these out, not that they're not related, but to try to emphasize each particular piece. Are you saying it would be more effective to put 1C together with 1A?

DR. LONG: No, no, no.

DR. FITZGERALD: Just change the order, 1A, 1C, 1B.

DR. LONG: Yes.

DR. FITZGERALD: Okay.

DR. LONG: I have a comment I want to make on 1C when you get there, and that will probably make it more clear.

DR. FITZGERALD: Right. Again, the order, as Suzanne reminded me, is based on how they are discussed in the report, but we can certainly look at changing, even in the report, to just create a better flow.

DR. LEONARD: Kevin, perhaps 1B could be expanded to include Francis' point, and Emily's. The pharmacogenetics technologies that are being developed have to be able to provide answers in a clinically timely manner with appropriate turnaround times. So that's part of a technologies development.

DR. FITZGERALD: We could say there, and Francis, tell me if this is okay, "on the timely development of clinically useful pharmacogenomics." Is that enough, or do we need to be more --

DR. COLLINS: I think you need something more explicit about the need to encourage technologies that give you rapid turnaround, cost-effective, point of care genotyping for pharmacogenomics, but that could fit into that particular recommendation just fine. It just needs to be fleshed out a little bit.

DR. FITZGERALD: Thank you.

Now, we've already talked a little about 1C, but let's -- go ahead, Rochelle.

DR. LONG: I was going to make a specific recommendation. There is a tool that NIH does have, a mechanism for clinical trial designers to actually list their ongoing trials, and that's ClinicalTrials.gov, and there have been numerous editorials in the New England Journal of Medicine. Everybody who does federally funded work must list there. Those who do industry-supported trials who want to be published in the New England Journal have to be listed there, and I think you could encourage its further use to enable collaborations where pharmacogenetic components could be added onto or even designed into clinical trials at the outset.

So, for example, the registry could list whether materials have been collected, whether DNA has been collected, whether it's been consented for pharmacogenetic studies. I view that as part and parcel of discovering -- how did you phrase it? -- the clinically validated knowledge that later on you want to implement into tests that are available rapidly at the point of care, but you've got to know what you're doing first, and you have to utilize the trials and studies that are already ongoing by adding that pharmacogenetic component, and a mechanism exists to do that if that registry were upgraded a bit, and those who run the registry are interested in doing it. They just need the recommendation or perhaps government encouragement to do it. It's a matter of collecting the right fields and the right encouraging and enabling research.

DR. FITZGERALD: That would be great. It's wonderful. The more specific we can get, if we can get concrete, that's wonderful. I have the sense that I think that could work.

DR. FERREIRA-GONZALEZ: Is that registry you design in your own institution the research and then you post it in that registry?

DR. LONG: ClinicalTrials.gov is run out of the National Library of Medicine. It is a project in itself, and anybody can post information to it. They make available the fields to do it. Then a trial designer must voluntarily submit that information.

DR. FERREIRA-GONZALEZ: For publication purposes. Is that tied to publications in a peer-reviewed journal?

DR. LONG: The journal editors got together and said we so much want to promote this kind of sharing of information that if you want to get into our top-drawer journal, you'd better be using that government registry.

DR. FERREIRA-GONZALEZ: But I think what we're trying to say here is that before you engage in these clinical trials, meet with certain people who do outcomes research or actually clinical trials that will actually develop these in a systematic way, that gather the right information that then can be used further down the road for applications for the FDA.

DR. LONG: I was thinking that the trials, in the context that I was presenting things, I thought the trials would be a source of discovery, discovering the information by doing the genetic evaluation, by looking at their genotypes, by looking at the medications that they're taking. You would discover the links that you later want to evaluate through the right kinds of outcomes or evidence-based studies, whether that should be implemented into clinical practice. But I consider this back at the basic discovery of those connections, that knowledge in the first place, and that's what I'm seeing under the basic and translational research recommendations here.

DR. FERREIRA-GONZALEZ: I thought that we were also looking to increase some of the values of these earlier clinical trials that will have --

DR. LONG: We're in total agreement there, increasing the value of research that's already getting done.

DR. FERREIRA-GONZALEZ: Exactly.

DR. FITZGERALD: Okay. Good.

Yes, Barbara?

DR. McGRATH: Under C, I was wondering if it might be useful to add in, under the list of clinical trial outcome research, also cost effectiveness there, to highlight that, since it's such a key point in this area.

The other thing I wondered about is although there's a separate section on ELSI, to maybe bring that into this section where you're talking about translational research, to highlight that as not just a separate type of research but that's embedded in translational research, the ELSI issues. So add in "cost effectiveness studies and ELSI issues" or "ELSI concerns" in C.

DR. FITZGERALD: Oh, I see. Okay. "Cost effectiveness and ELSI."

Now, with the ClinicalTrials.gov website, obviously that information doesn't get put in there, too. Or could that?

DR. LONG: "That information" meaning --

DR. FITZGERALD: Cost effectiveness, ELSI issues.

DR. LONG: I would say no. Think of it as a registry that simply presents to the world, we, a group of researchers or a company are planning to do a trial or we are doing a trial, this is what we are studying, this is who you would contact, these are the enrollment criteria, this is what's being collected. So it enables researchers to make connections. It doesn't dictate what kind of research is done. It's not a funding mechanism. It's a directory.

DR. FITZGERALD: We can still put that in, but we'll make sure that some of that breaks out and goes in one direction and others is there for people to --

DR. FERREIRA-GONZALEZ: I think it's different. What we're trying to say here is that we want to encourage researchers to coordinate with clinical trials outcome researchers while they're doing their study design. What you're talking about is just listing what other people are doing so they can actually communicate with each other, hopefully not even repeat some of these studies.

DR. FITZGERALD: Right. That works.

DR. RANDHAWA: Perhaps I came in late, but this discussion is getting into Recommendation 3, which deals with clinical validity and utility. So the effectiveness, cost effectiveness, ELSI issues are certainly part of that also. So I wasn't sure are we meshing and combining all the recommendations, or are we going to keep them in different places?

DR. FITZGERALD: No. We're trying to be as discrete as possible. On the other hand, we're trying to make sure we do the proper amount of emphasis on the various issues. That's why we're going through this now. If we need to jump back and forth a little bit, we can do that in this section. Now, we'll also probably revisit some of these issues in other sections as they regard application, but that's okay too. So we'll do that.

Look at 1D. "Research that could lead to the development of a pharmacogenomics test requiring FDA review should be planned with the goal of meeting FDA quality of evidence standards so that the results can be used in support of a premarket review application. NIH should encourage investigators to consult FDA when their research reaches a pivotal stage, and NIH could encourage the conduct of methodologically sound and statistically rigorous studies by giving higher priority scores to studies that are designed to satisfy FDA quality of evidence standards."

Again, this is a recommendation in an attempt to tie things together, which we thought was an important thing to do.

Is everybody all right with that? Wonderful.

DR. LONG: That's just a little bit awkward in that NIH doesn't actually give priority scores. NIH assembles review panels that do peer review. I would say funding decisions should give weight to satisfying FDA quality of evidence standards.

DR. COLLINS: I think if we just drop the word "scores" --

DR. LONG: "Priority scores."

DR. COLLINS: Because it sounds like NIH is going to overrule the study section.

DR. FITZGERALD: We like anything that makes them shorter. That's good.

Andrea?

DR. FERREIRA-GONZALEZ: Do you think here that maybe something education to research, doing translational research and how to conduct some of these statistical studies?

DR. FITZGERALD: We have some other educational ones.

DR. FERREIRA-GONZALEZ: Through workshops or some other venue?

DR. LONG: I hear you. Let me try to figure out the best efficient way to do that and get it inserted at the right time.

DR. COLLINS: I think that does come up in the later recommendations.

DR. FITZGERALD: It does, later on. We do get to education of the researchers.

Michael, you had something?

DR. AMOS: I just want to get back to Mr. Rollins' point before about the testing accuracy. Is that captured in any of these four subcategories? Because I really think that the standardization of

the testing and the accuracy of the testing really need to be evaluated. Like I said before, there are only a handful of diagnostic tests with actual standard reference materials.

DR. FITZGERALD: Well, when we get to Recommendation 3, we talk about validity and utility, and we could certainly add in accuracy at that point. That might fit I think the concerns on that. Is that okay?

Joe?

DR. TELFAIR: It's a question, which is more a point of clarification to ask to the NIH. I guess I have always been under the assumption, in looking at the way studies are reviewed, that priorities are already given to those that are methodologically sound and statistically rigorous already. I mean, I thought that was already in existence, and I'm wondering if that's true, then maybe the wording should be something along the lines of if it's going to be integration, that it should continue to enforce or continue to remind people. I mean, if it's already there, it seems a bit unnecessary to say they should do something they're already doing.

DR. LONG: I think you're correct that instructions to review panels are to give the higher scores to the statistically rigorous well-designed studies. You're right. I believe, and I didn't craft this original recommendation, that there was some intent here that the FDA saw specific and unique needs, and sometimes they felt that the weight should go into funding the types of studies they need to see done. Am I accurate? So I think that's the little FDA angle that made this one different. But you're right, I think review groups already give the best scores for merit to the most well-designed studies.

DR. FITZGERALD: Again, we can reword this to make this more clear, but I think the implication is that what's in the first paragraph is what's considered to be methodologically sound. How do we put it that way? And statistically rigorous. That's not necessarily thought to be as strong at the moment.

DR. MANSFIELD: Hi. It's Liz Mansfield. I'm from the FDA. I would just encourage you not to put the cart before the horse here, that studies are typically reviewed and funded prior to having been done, and the way that this is written, it appears that they would only seek FDA advice after they had reached a certain point. So I'm not sure how review boards could say that something was meeting FDA specifics if the studies had never even started yet.

DR. FITZGERALD: Right. Well, in the second paragraph we have "NIH should encourage investigators to consult FDA when their research reaches a pivotal stage." Is that what you're --

DR. MANSFIELD: Right, but then the next section says you would encourage funding to studies that are designed to satisfy FDA quality of evidence standards, and I think those may be somewhat in conflict with each other. As far as I understand, you tend to get funding before you reach pivotal stages.

PARTICIPANT: So drop the last paragraph there?

DR. MANSFIELD: Perhaps. I agree that you're on the right track. I just think that it will be hard to say that this will meet FDA quality standards before the funding has been given.

DR. FITZGERALD: Emily?

DR. WINN-DEEN: I think what we were trying to get to is the next level of study beyond the tantalizing early results study. So now you're going to design a study that really is a validation study, and having been into FDA once or twice and been told that one of the things that FDA would like to see is some good published studies done independent from the manufacturer indicating that that marker has clinical utility and validity, I think what we were trying to get to is to encourage people doing those studies separate from whatever company might sponsor a device, to do those in a rigorous way so that FDA could consider that as a reasonable piece of literature.

DR. MANSFIELD: Yes, I think that's entirely reasonable. Maybe just a little clarification here, then.

DR. FITZGERALD: Okay. So when you read this, you were hearing that the third paragraph sort of stood out on its own, and I think that's what we're getting from both Joe and you. So that third paragraph is leading people away from the first two somehow. Okay. Great.

In 2A, this is development of pharmacogenomics products. "Health and Human Services should provide FDA with the necessary resources to develop guidance documents about best practices for the co-development of pharmacogenomics drugs and diagnostics. This guidance should promote collaboration between the drug and diagnostic industries and clarify the review process for co-developed products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be."

Oh, in your executive summary this is 2D. It got moved up, if the list is actually somehow some kind of prioritization, which it isn't. But in any case, it's now 2A. Okay?

DR. LEONARD: Kevin, can I ask a question here?

DR. FITZGERALD: Sure.

DR. LEONARD: I thought FDA had a draft guidance on the co-development. Hasn't this been done?

DR. MANSFIELD: It's actually a white paper right now, headed towards draft guidance status.

DR. LEONARD: So if this is underway, do you need to have a recommendation on this?

DR. FITZGERALD: I thought the sense of the task force was that this could only help move this process forward, that there was a desire to make sure that this was emphasized.

DR. MANSFIELD: Yes, there is a desire to get the draft guidance out, but it has been previously released as a white paper and not a draft guidance.

DR. FITZGERALD: Good.

This is 2B. "FDA should identify research opportunities relating to the co-development of pharmacogenomics products. FDA could encourage and facilitate the conduct of this research through its Critical Path Initiative."

Then 2C. "HHS should advance the further development of abandoned drugs by facilitating access to information about such drugs. Incentives will be needed to encourage the voluntary

submission of proprietary data by pharmaceutical companies." Again, trying to address some of that gap problem that we had identified in the issues earlier. All right? Great.

Then what is now 2D.

Sorry, Gurvaneet. Back on 2C?

DR. RANDHAWA: Yes. It's not clear here where that data will be housed. It says "to encourage manufacturers to submit proprietary data." To whom? Where would that data be housed?

DR. FITZGERALD: Right. It doesn't say that there either, right?

DR. LONG: It's housed at FDA right now, right? Voluntary genomic data.

DR. FITZGERALD: Do you have a specific place that you want it to be housed, or is FDA okay? Because that's where it is housed now, right?

DR. RANDHAWA: Well, if the intent is to try and have the database available to others to take the technology further, I'm not sure that that's going to be feasible. So I wasn't quite sure what the intent was after the manufacturers release it. If it still stays in FDA and it's not accessible to others, would it meet the purposes?

DR. FITZGERALD: I see.

DR. LONG: Can you ask for development of incentives to encourage the eventual release? Because right now there are no plans to release any of that, right?

DR. MANSFIELD: The voluntary genomic data submissions? No. I suppose any company that's submitting could release it if they wanted to.

DR. FITZGERALD: Identify yourself, please.

DR. RUDMAN: Allen Rudman, FDA, CDER. FDA has a voluntary genomic data submission process, but the information that comes into it is confidential. So that helps FDA. It doesn't necessarily help the rest of the industry or academia. So I think what we're talking about here is a process for making it public.

DR. FITZGERALD: Right.

DR. RUDMAN: So then how we go about that, that could be publications or something else, but that's what really needs to be determined.

DR. MANSFIELD: As far as incentives, I think you would want to make some concrete suggestions of what those incentives might be.

DR. FITZGERALD: Now, you want those in this report or we can just put that forward to the Secretary and allow the Secretary to make those determinations?

DR. MANSFIELD: That's up to you.

DR. LEONARD: Can I ask a question here? If it's in a blended drug, would the drug company have done a submission to the FDA? If they'd gone through trials, are we talking about something that would even be submitted to the FDA here? I don't think so.

DR. MANSFIELD: Drugs can be abandoned at many stages, and they may have been submitted to FDA.

DR. LEONARD: But they may not have.

DR. MANSFIELD: But they may have been abandoned prior to that in developmental stages, clinical stages. Yes.

DR. LEONARD: So we may not be capturing all the abandoned drugs if we're talking about data that's submitted to the FDA. So I think we need to incentivize the drug companies to further develop or move forward abandoned drugs using pharmacogenetic technologies, and I don't know what those incentives would be. You'd have to ask drug companies what would incentivize them to move drugs forward for a smaller market than what they were originally anticipating.

DR. FITZGERALD: I'm not sure that we need here to -- because there are a variety of reasons that one could abandon a drug in the development process. Not all drugs are abandoned because of a population problem, they just can't get enough people or they don't get enough effectiveness. Do we need to capture all "abandoned drugs," or are we trying to incentivize the ones that, in fact, might fit this profile of being able to target a smaller subpopulation?

DR. EVANS: I think we should be careful about making recommendations that aren't feasible or that we have no inkling of how we could ever incentivize for it. Unless we have some inkling about how one could incentivize drug companies to make such information public, I'm concerned that we dilute our recommendations if we just say, oh, you should do this, that you should incentivize it without any idea of --

DR. FITZGERALD: Right. In the fact-finding stage that's next, we could certainly ask what those concrete incentives would be. We could certainly ask industry what they would consider incentives.

DR. FERREIRA-GONZALEZ: Is there a concern now that we need to keep this here and not just take it out?

DR. LONG: I think that second paragraph is really valuable, because I think the individuals that I know at the FDA have all worked hard with industry for the voluntary submission of genomics data, and to reinforce that voluntary submission of proprietary data to an agency that can gain in its knowledge as it makes decisions about drug approvals, this is not for abandoned drugs, this is for things that are in development now. That's a wonderful thing.

Coming from the NIH side of the fence, I would love to promote that it ultimately be made public, but I have to be realistic. How many companies are going to voluntarily submit data to the FDA that they think they're going to be forced to make public? That's going to have a very chilling effect on the voluntary status of the submission system.

So I understand the competing nature of the issues here. What you have written is good in that second paragraph. I guess the confusion is it applies to more than just abandoned drugs. It applies to things in development now.

DR. FITZGERALD: It certainly could, right.

DR. LONG: It does, it does.

DR. FITZGERALD: It does. But the question is can we narrow the scope?

DR. LONG: I think your fact-finding suggestion so the group can make careful recommendations in concert with the system that already exists is a good idea.

DR. FITZGERALD: Okay.

DR. LONG: You may want to fact-find more before you do it, or you'll drill down too deep and have unintended consequences, disrupting something good. Would you agree?

DR. FITZGERALD: Well, I think we can certainly, in looking for incentives, discover that. That would help elucidate that.

Yes, Michael?

DR. AMOS: If the committee is saying that this is something that's absolutely needed to move pharmacogenomics along and you can't identify any real way of doing it with the existing data, should you also consider another recommendation for implementing that if this is not the only way to do it?

DR. FITZGERALD: That's a good point. So you're saying if this turns out to be one of those things that's not implementable, then what do we do? Right?

DR. AMOS: Right.

DR. FITZGERALD: Okay. That's definitely a conditional statement. So since we don't know yet whether the "if" is true, I don't think we can quite get to the "then." But that's certainly something we'll have to look at. If incentives do not exist and it's not implementable, I think we'd have to then address that particular situation. Okay, that's a good point.

DR. EVANS: So what's the resolution, then?

DR. FITZGERALD: So what we're doing is saying the resolution, in a sense, can I think stand at the moment, but we need to go and find what those incentives might be so that we can be a little bit more specific in recommending to the Secretary this is what we have discovered from industry or from our fact-finding; not to say that you have to do it this way, but we would at least be able to make some specific concrete recommendations along those lines, such as what we do in some of these other recommendations where we say such and such is already underway. We could say these are things that have already been identified as possible incentives.

Debra?

DR. LEONARD: But these seem to be two different recommendations that are bundled together here. One is abandoned drugs and encouraging industry to move abandoned drugs forward if they're abandoned because of an adverse drug reaction in a small population but it shows effectiveness in those who don't have the adverse reaction, or other things that pharmacogenetic testing could help with to identify the populations that will be helped by these abandoned drugs.

Then the incentives part really applies to all drugs. I mean, you want the pharmacogenetic information for any drug, not just abandoned ones. So it seems like there are two things here that are being mixed together inappropriately.

DR. FITZGERALD: Okay. I think what we were trying to do was to narrow this down, but we could broaden it if the committee thinks this is better. "HHS should advance the further development of drugs by facilitating access to information about incentives that would be needed to encourage voluntary submission." We could just drop "abandoned." We don't need to have that in there.

Emily?

DR. WINN-DEEN: Well, I think the original discussion about this was this whole concept of drug rescue. Either there are perfectly good drugs out there where if you could eliminate the few individuals who have bad reactions to them would be great for the majority of people for whom they are effective. I think we were trying to take a very narrow, defined subset where we thought pharma might not be as sensitive about it. Okay, your drug was abandoned or it was pulled off the market anyway, so you're making no money off of this. Is there some way that pharmacogenetics could help bring that back for the benefit of patients? So I don't think this was ever intended to be a broad recommendation that every drug and every pharma company had to collect this information and reveal it to the public. It was really in its initial discussion I think focused on this small subset of things that are off the market now for one reason or another, so the stakes are pretty low from the pharma company point of view because it's making no money for them right now, and this might be a way to resurrect something.

DR. LONG: I hear what you're saying. You're saying this is the data that wouldn't have been submitted ordinarily, while other data would have been.

DR. FITZGERALD: The idea was to pick a battleground --

DR. LEONARD: I understand what Emily is saying, which is what I was saying about this first part of this slide 39. By facilitating access to information about such drugs, I think facilitating information to whom, to do what with? It just is very vague. I mean, basically what you want to do is encourage the pharmaceutical companies to move these drugs forward by using pharmacogenetics. Do they have to give proprietary information to anybody?

DR. WINN-DEEN: My experience with most pharma companies is that once it's done, it's done from their point of view. So the chance for them to resurrect it is not as good. It's an emotional thing within the company. It's much more likely that some other company would take it on and buy the rights to that drug and then do these studies and try and show that although the drug was not safe for the general population, if you do this test, that it then could be used effectively.

DR. LEONARD: So is this recommendation capturing what needs to be done? I don't think it is.

DR. FITZGERALD: One minute, before we get too deeply enmeshed in one. I'm going to pull a Reed and we're going to flag this for just a moment, and we'll come back to this if we have time at the end, but we're definitely going to say this is a problematic recommendation. If we don't get back to it today, we'll certainly try to rework it in such a way as to make it more clear what the intent of the recommendation is and how it addresses the issue, because we're running a little behind.

DR. TUCKSON: I think what we can do, by the way, just to help out our chairperson, is if you could just jot on a little piece of paper what you think it ought to say, just try to give him the solution to the problem and then hand that in and he can look at it at the break.

DR. FITZGERALD: That's great. We can do that.

So going on to 2D, this was one that was flagged as a high priority by the task force, that "FDA should amend the Humanitarian Device Exemption Regulation so that incentives for the development of orphan drugs are extended to pharmacogenomic tests that are intended to be used in conjunction with the orphan drugs."

DR. MANSFIELD: FDA again. First of all, I want to make sure that everybody understands the Humanitarian Device Exemption extends to tests that are intended to be run on 4,000 people or less or on a population of 4,000 or less, depending on how you interpret the rule. There's no clinical validity required in order to have a Humanitarian Device Exemption, and that is based on the assumption that a potentially flawed test is better than no test. I suppose you could rewrite the regulation to model it differently, but I'm not sure that's where you want to go with orphan drugs right now. I also think that if you extended it to the 200,000 that orphan drugs are now allowed, you would create an extremely unlevel playing field for genetics versus every other kind of test that would probably be somewhat upsetting to the rest of the community.

DR. FITZGERALD: So now, in doing what this says, I understand what you just mentioned. This apparently would change the regs for tests so that they would have to have clinical utility, right? Because they would be falling under the orphan drug designation, right?

DR. MANSFIELD: I'm saying the current Humanitarian Device Exemption requires just an assumption of clinical validity, not utility. So my feeling on reading this was that you simply wanted to up the number of patients who could receive the test under this exemption.

DR. FITZGERALD: If it's done in conjunction with an orphan drug.

DR. MANSFIELD: Right. So what I'm suggesting is that as the exemption is written now, you are running a test on up to 200,000 people for which you have no clear clinical validity with the assumption that the test may be flawed and that a flawed test is better than no test.

DR. FITZGERALD: Thank you. We may have to go back and look at this one also. That's good information. We'll also flag this one, too, to possibly go back to.

Now we're going to go down to that whole area of clinical validity and utility of pharmacogenomics, and the people who mentioned accuracy can recommend wherever they want that to be first put in. But this is our first recommendation in this area, that "HHS should provide AHRQ, CDC, NIH with additional funds to identify pharmacogenomics technologies that are important from a public health standpoint and support efforts to address gaps in evidence for which clinical validity and utility evidence is lacking. So CDC's EGAPP Working Group and HuGENet and AHRQ's EPC program may be appropriate mechanisms or models for identifying such technologies and specific evidentiary and research needs." Again this was flagged by the task force as a key recommendation.

DR. ROLLINS: In addition to clinical validity and clinical evidence, we've got to somehow incorporate measures of accuracy, number one. Number two, also utility evidence, I think we need to go further than that. Some people think that pharmacogenomic tests are diagnostic tests.

Looking at diagnostic tests, we look at accuracy. Also, we look at how is this test going to be used in terms of management of the patient. I think the wording "management" is going to have to be incorporated in this because if I'm evaluating a particular technology, not only CMS but also other insurers, if tests are lacking in terms of measures of accuracy, at least it should be demonstrated that if a physician uses that test and the results of that test will dictate his or her change in management of the patient, if there's some way we can incorporate "management," because that's what we look at when we look at a diagnostic test, how does this test alter or continue the management of that patient.

DR. FITZGERALD: Now, the management issue, we want to put that in the R&D here, or may that be later on in the application?

DR. ROLLINS: Well, I looked, and it's also applicable to number 7, but if the studies cannot show that this test helps in the management of the patient, then it would be difficult to say how it's applicable in terms of a clinical application. You might even look at a decision tree. Depending on the results of the test, does a physician do A, B, or C? But as I said, it's all involved in the management of the patient.

DR. BRADLEY: I just wanted to bring up that to address Jim's issues about accuracy, the easiest solution here would just be to talk about analytic and clinical validity, the way you do in the narrative, because that will cover analytic sensitivity and specificity and reproducibility and all of that, and accuracy.

DR. FITZGERALD: Just one second. What page are you on?

PARTICIPANT: Thirty.

DR. FITZGERALD: Let me just read what we have in the report, just for clarification purposes. If you look on page 30 of the draft report, under the section on clinical validity and utility, I'm not saying we can't still make this more specific, but it says, "Clinical validity refers to the accuracy with which a test predicts a given clinical outcome. Clinical utility refers to the ability of a pharmacogenomic test to inform clinical decisionmaking," which might include management, "prevent adverse health outcomes and predict outcomes considered important to individuals and families." So maybe where we're not getting the thing here is we're not getting this into the recommendation, or not everybody understands these terms in the same way.

Does that capture, though, some of what -- go ahead, Linda.

DR. BRADLEY: Well, I was just going to say that the sentence before that was the description of analytic validity, which I think is very important in this context.

DR. FITZGERALD: Right, okay.

DR. PAREKH: I was just going to say I think clinical utility as it's defined encompasses management. So I was going to ask James about that. It seems like it's encompassed in utility.

DR. FITZGERALD: Would we need to make that clear in the recommendation, or is it okay to make that clear in the report?

DR. ROLLINS: I know that when we do technology assessments, for example, somebody has submitted cytogenetic testing and they've submitted to us a lot of articles talking about a specific

marker, but they don't connect or they don't link how the results of that marker are going to result in the management of the patient or change in the management of the patient, that's a link that I don't know if we're stressing hard enough, but there's got to be some kind of link between the results and how that patient is going to be managed depending on the results of that particular test.

PARTICIPANT: But that is clinical utility.

DR. PAREKH: I'm just saying if you ask a clinician and you ask them about clinical utility, that's exactly what that is. It's the management of the patient.

DR. FITZGERALD: Right. We can work to make sure that's clear someplace.

DR. FERREIRA-GONZALEZ: So the idea would be to add the analytical and clinical validity and utility evidence.

DR. FITZGERALD: The analytical thing is easy to do, just put "analytical" in there along with clinical.

DR. FERREIRA-GONZALEZ: So that would take care of the accuracy.

DR. FITZGERALD: Right.

DR. RANDHAWA: I support Linda's suggestion. So if the intent of this bullet was to make it focus on clinical outcomes and not analytic validity, then I certainly think we need to capture getting that information. So perhaps you could do that in the first recommendation where you're talking about basic research. There's no mention about analytic validity here in the basic and translational research. So if the intent of this recommendation was to focus only on the clinical outcomes, then to make sure we don't lose analytic validity anywhere in these recommendations, we could perhaps make it more specific in the first recommendation.

DR. FITZGERALD: The first being which one? 1A?

DR. RANDHAWA: The basic and translational research which NIH should support, the basic. In my reading here, when we're developing new knowledge about a test, there is no specific language about analytic performance of the test. So if the intent is to leave this third recommendation more focused on the clinical outcomes, then we could be more specific in laying out the analytic performance in the initial studies.

DR. FITZGERALD: So what you're saying is in either 1A, 1B, 1C or 1D, put it in there?

DR. RANDHAWA: Right.

DR. FITZGERALD: Okay. Following up on Reed's suggestion, pick one, write where it would go, and at the break I'd be happy to get back to that.

DR. RANDHAWA: No problem.

The second comment was I'm speaking here from AHRQ's perspective. The evidence-based practice center program is identified, but when we do these meta-analyses or reports or technology assessments, they're useful in pointing out where the gaps in the evidence are, or

where the research needs are. They are not amenable to creating new knowledge or doing new outcomes research to fill in those gaps. I'm reading through these A, B and C, and only within C we have a sub-sector there where public and private health plans should facilitate the generation of new knowledge, but here we're making it conditional, in certain circumstances.

So what are the mechanisms for routinely creating new knowledge for clinical outcomes? We don't really specify that in any of these three, A, B or C here. We could make A more clear by specifying both dimensions. One is appraisal of the existing evidence and pointing out research gaps, but B would then be identifying mechanisms to fill those gaps, which should be programs like, say, the DEcIDE network at AHRQ, or the CERT program at AHRQ, which are more for creating new evidence as opposed to just appraising the existing evidence.

DR. FITZGERALD: As we did here, we're happy to be specific. But would you want that here? It could probably also go in 3C.

DR. RANDHAWA: It could go anywhere. I just wanted to raise it that I don't find it anywhere in A, B or C.

DR. FITZGERALD: Okay. So we could either add that here, or we could add it to 3C. It looks like that would be a good place. Okay, thank you.

3B, again one that was flagged by the task force as a higher priority. "FDA should encourage manufacturers to submit clinical utility data as part of their premarket applications and post-market surveillance. Request manufacturers' permission to make these data available to the public. Manufacturers should disseminate any significant and non-significant findings on the clinical validity and utility of pharmacogenomic technologies, e.g. through publication in peer-reviewed journals."

Yes, Emily?

DR. WINN-DEEN: I guess reading this again, sort of in isolation, which manufacturers are we talking about? Drug manufacturers? Device manufacturers? I just think it needs a little clarification.

DR. FITZGERALD: We need to clarify.

DR. MANSFIELD: I'm not familiar with the regulations of drugs enough to really say, but I know for devices that evidence of clinical utility is currently not a strict requirement. Many companies who are performing these tests would like to get them to market as quickly as possible, and it's my assumption that that's what the committee would like too. If you delay getting to market by enforcing the provision of strict clinical utility, you may be working against yourself. Some supposition of clinical utility is needed, but actual outcome studies and so on generally take a long time and are not traditionally done for devices.

DR. FITZGERALD: Debra? Or Allen. Your mike is not working, I don't think. Is it on?

DR. RUDMAN: It's on.

DR. FITZGERALD: Okay, there it is.

DR. RUDMAN: A minor point. You may want to include that FDA should encourage the manufacturers to submit pharmacogenetics. Right now it's just all clinical utility data.

DR. FITZGERALD: Okay.

Debra, did you have something too?

DR. LEONARD: I wanted to point out to the committee that in September, CDER development a table of biomarkers and pharmacogenetics tests that actually has an indication in three levels. One is that it's informational, the second is that it's recommended, and the third that testing is required. It provides information with the drug label, and it has references in that table to the studies that have been done to support the pharmacogenetic test relative to a specific drug. It was initiated in September, it was updated in October, and I think this committee should encourage CDER to continue to update that table of information because it's extremely useful as a house system. When we found that, it actually supported some of the pharmacogenetic implementation stuff that we were doing.

So in this recommendation, the FDA is actually making this information, or CDER -- I assume CDER is part of the FDA? I have problems with all the acronyms of knowing who is what, but it says CDER on the top of this table thing. So the FDA is actually doing this, and that's great.

DR. FITZGERALD: We could put that down, if it's okay, where we have "e.g., through publication and peer-reviewed journals," or through the table that is being --

DR. LEONARD: Through the CDER website.

DR. FITZGERALD: Right, the CDER website.

Just for clarification again, to address your issue, Elizabeth. If this said, "FDA should encourage drug manufacturers to submit," that would take the focus and put it on the drug and we wouldn't have the device issue. Is that correct?

DR. MANSFIELD: I think so, yes.

DR. FITZGERALD: And maybe that's the specification, and then we could do the pharmacogenomic and pharmacogenetic information as well as the clinical utility data.

DR. RUDMAN: I would also make one other recommendation here. It says, "to request manufacturers' permission to make this data available to the public." I certainly would encourage this, but I'm not sure what you mean by "request." When the FDA makes a request, it's viewed sometimes in a regulatory manner. So maybe just the wording needs to be changed.

DR. FITZGERALD: "Encouraged"?

DR. RUDMAN: "Encouraged."

DR. FITZGERALD: Okay, good. Thank you. We don't want to intimidate anyone, except the people here so we keep moving.

Here we go, draft Recommendation 3C. "In certain circumstances, public and private health plans should facilitate the generation of knowledge by conditioning payment of

pharmacogenomic technologies on a commitment by test developers to collect data on the clinical validity and clinical utility of pharmacogenomic technologies." Did I read that correctly? It didn't sound good. Anyway, "CMS' draft coverage with evidence development initiative may serve as a model for this practice." We're good on that one. Sylvia is questioning.

MS. AU: I'm a little concerned because you're mixing payment with clinical research. Is this clinical research needing informed consent, and if the person doesn't consent they don't get payment for their treatment?

DR. FITZGERALD: I guess the lack of clarity here is in the "in certain circumstances." So considering the question that you just raised, I think we need to potentially address that problem.

MS. AU: And whether it's identified data or it's unidentified data.

DR. FITZGERALD: Okay, let's flag that one. Since we put it out here now, we've got to deal with those issues. In fact, Sylvia, if you could just jot something down for the break, that would be great and we'll see if we can work that around.

Can we move to 4A? Now we're moving on to the research databases. "HHS should work with the private sector to improve data sharing and interoperability among research, regulatory and health record and claims databases. 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. Comparable efforts to standardize phenotypic data are also needed." Again, this was flagged by the task force committee as extremely important. This tries to get at that question that we mentioned before about how the different groups and databases can talk to one another. Is everybody happy with this?

Then 4B. "As the data are shared, the privacy of patients and research subjects should continue to be of paramount concern, and HHS should take steps to ensure that the confidentiality of their data is not compromised," again flagged by the task force committee, and again this goes back to that balance I mentioned before that we're trying to strike.

Rochelle?

DR. LONG: I have an observation. I don't know the solution. But if privacy is of paramount concern, this will lessen sharing of data for research purposes.

DR. FITZGERALD: Yes, it will. That was the tension I mentioned earlier.

DR. LONG: Clearly, this is written to allow institutions to hold on to as much data as possible when it comes time to deposit it into databases. This will give them reason to not want to share their data. Is that exactly the way you want to push it? Please comment, others.

DR. COLLINS: I'm glad Rochelle brought this up because I think this is going to be an issue for all kinds of studies, and pharmacogenomics will be one example. Clearly, privacy and confidentiality are an absolutely important principle, but if one decides that that is the only principle, then basically you have no research databases at all because somehow they might leak or somebody might get access who shouldn't. This is worded in a way that almost makes it sound like that would be your intention. So I think perhaps choosing your wording a little more carefully here to say that confidentiality and privacy are critical principles and every effort should

be made to maintain them while also making certain that research can go forward by providing access to qualified scientific researchers.

DR. FITZGERALD: Reed, go ahead.

DR. TUCKSON: I think that is a very well crafted solution here, and I think the committee knows it's obvious. We have to push hard on the privacy paramount attentiveness. I know that a lot of the stuff that's happening in America's health information community which we talked about earlier is really threatened by the concern of the public around this privacy and confidentiality deal, and in some ways if we're not attentive, it makes the whole agenda a non-starter.

I think the way that Francis phrased it is really the way to get at it, and if somebody got that language, I hope that you're writing it down. If not, he needs to say it again.

DR. FITZGERALD: My only fear, Francis, is that the way you stated it does the exact reverse, just listening to the way you phrased it. This is an important concern, but the research must go forward. The "must" is the key thing. I agree with you that we've got to balance this in our language, but --

DR. FERREIRA-GONZALEZ: I think we currently have federal regulations to protect the privacy of human subjects that enter some of this research that can be used into these databases or clinical validity, et cetera, where you use codified or you deidentify this information. So maybe using what is currently in the regulations now to this would suffice that we assure some of the privacy of these individuals, but then we're allowed to continue for the research.

MR. DANNENFELSER: I think that was the basic same point. Can't the demographic data be shared while still protecting the privacy of the individuals?

DR. FITZGERALD: Joe?

DR. TELFAIR: This is a little bit outside of my purview, but I would suggest that maybe you have a couple of e.g. on some of these things. There are models that exist, like the Clinical Networks, that sort of thing, that may be considered in terms of how they go about doing that data sharing and ultimately protect privacy. So I would maybe say, e.g., along Clinical Network lines.

DR. FITZGERALD: Okay, we can put that. I think Francis was concerned with the language, where is the bottom line going to be, and I think what we can do is work on that to just show this is going to be a continuing tension but the question is can it be a creative tension or is this going to be a destructive tension, and hopefully we'll make it creative.

We are scheduled right now for a break. We'll do 5, and then we'll take our break.

FDA guidance for population subgroup data, draft Recommendation number 5. "Race and ethnicity categories should not be used alone when analyzing differences in drug response. FDA should develop guidance that encourages the collection and analysis of genetic and other biological factors that may better explain differences in drug response. When drugs are shown to be effective in certain racial and ethnic subpopulations, FDA should require manufacturers to conduct additional studies to identify biological markers that underlie the differential drug response."

Yes, Jim?

DR. EVANS: The only problem I have with that is the requiring manufacturers to conduct these studies. These are extraordinarily reasons that range from environment to genetic factors that may be responsible for different racial/ethnic categories responding differently, and I think that by demanding an explanation for that when those things are so complex that they've proven extraordinarily difficult to work out, I just think that's overstating it.

DR. FITZGERALD: Let me see if we can't get at this tension too in a somewhat creative way, because I understand what you're saying. It says here "should require manufacturers to conduct additional studies." It doesn't say "require manufacturers to identify." So you don't have to get the answer.

DR. EVANS: Well, I don't know. I'd argue that if you do show in a statistically rigorous way that a certain group, be they people with blonde hair or people who live in Love Canal, respond differently to a different drug, I think it's laudable to look for those, but I'm not sure if requiring those studies is something that makes a lot of sense from the FDA's standpoint.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think I'm not sure either of what this is trying to do. When you pile all those burdens on the manufacturer, it really seems to me to have a stultifying effect for bringing the product to market, and I'm not sure what advantage you get here.

DR. FITZGERALD: The sense I think we were trying to capture here, and obviously many of you are aware of this in the literature, the discussions going on about the potential effects of pharmacogenomics, that rather than ameliorating racial categories and differences and particularly disparities in health care delivery, that these would actually exacerbate them. But you're right, we could probably take out "require" and --

DR. EVANS: I think you address it very well in the first two paragraphs, and I just don't think the third paragraph adds much and does make it rather confining. So I think just taking out the third paragraph then makes it very reasonable.

DR. FITZGERALD: Allen?

DR. RUDMAN: As you know, there is a drug out there, BiDil, that's currently been approved for that. So I'm not sure what you're exactly recommending. Are you recommending that it be taken off the market?

DR. FITZGERALD: No, no. The recommendation is that the -- again, there have been articles addressing this issue. If one did a study of the population that BiDil is supposed to target, one would still probably find a spectrum of response to that drug, and one might even find a response to the BiDil combination outside of that particular group where you have high responders. So the question here is, is using the category African American something that is socially problematic, problematic to a particular underserved group as it is, in such a way as to say this social detriment raises issues that we need to address, not necessarily by taking the drug off the market but perhaps by better informing ourselves as to what it is that delineates that population for which that particular drug is actually beneficial, or significantly beneficial. That's the intent.

DR. RUDMAN: Okay. I would make a recommendation. I would actually make a comment first. Some of these racial and other criteria are in international agreements. That's just one comment.

But I think what you're really aiming for is to encourage this to move forward from a racial to a genomic, pharmacogenomic --

DR. FITZGERALD: Absolutely. That's the idea.

DR. RUDMAN: So maybe it can be revised to kind of say that. So where race and ethnicity are found to be determining factors, pharmacogenomics should be looked into. I'm not sure if I'm getting to where you're going.

DR. FITZGERALD: I think we're trying to get that in the second paragraph for sure. But in any case, one of the recommendations is to just cut out paragraph three, which is what you're saying.

DR. TUCKSON: I think, if I understand where we really are here, it's that when you make an interesting observation, that there ought to be efforts that either facilitate the further research into what is actually going on or the recommendation is you're trying to make sure there is a database made available to support such research, and it looks like you're trying to use the FDA as a way of facilitating access to the data that researchers can then use downstream. The question ultimately becomes that everyone would say that it is a good thing to learn more about what this observation means, and that's mother, God and country that we ought to say yes to.

The second question is can you put on the back of the manufacturer a requirement to do that, and I think we're rejecting that in losing paragraph three. The second question is can you put that on the back of the FDA to provide some mechanisms for that to occur, and it seems to me the FDA is saying that may be problematic as well, and I'm not sure what your answer is.

So I think what we are left with is this is an important thing to study and people ought to pay attention to it in the best of all worlds. Researchers will go after it, NIH will give money to go after it, smart people will decide to think about it.

DR. FITZGERALD: In that light, if we put HHS in instead of FDA should develop guidance, that takes the burden off FDA specifically, which may be a good thing to do, but it allows greater breadth.

Yes, Francis, and then Elizabeth.

DR. COLLINS: Let's not undercut this too severely. I mean, many people do believe that the BiDil experience was an unfortunate one, and I happen to be one of those, that the reification of racial categories in a decision about who gets this drug or that drug both does a disservice to the public health because it substitutes an imperfect proxy for what may be much more specific information that just wasn't collected that might predict who is going to respond and who isn't, and of course it has the other negative consequence of implying to the general public that race is something that is biologically determinant, and because the FDA has now approved this drug for African Americans, they must be somehow different, which we know is a vast overstatement of the biological facts of the matter.

So I think it is highly appropriate in this set of recommendations to put something in to discourage that kind of occurrence again, and I think FDA appropriately should be asked to

develop guidance, just as your second paragraph says here, to encourage manufacturers who are putting forward this kind of test to do better next time.

DR. FITZGERALD: Elizabeth?

DR. MANSFIELD: I guess I have somewhat of a conflicting opinion. I think that race and ethnicity are certainly very imperfect surrogates. On the other hand, do we want to say, if that's the only surrogate you can come up with, forget it, you don't have a drug? I'm not trying to say that you did say that. I'm saying my own opinion.

DR. FITZGERALD: Right, right.

Joe?

DR. TELFAIR: Knowing that this is an issue, I'm liking the wording that you're using. I think "surrogate" was the word you used. "Proxy" was a word you used. I mean, really, it's what is the meaning behind this and what is the intent, and what I'm saying is the intent is along the lines that there are areas in which disparities occur by which there is an unevenness in terms of how these things are done.

Maybe the point here is to acknowledge that with the first two paragraphs, but then to refer to and put something in a little bit stronger language in your ELSI section related to this, and that would then get at the intent issue as well. You can start with the intent here and leave it at that with the first two paragraphs, I would agree with my colleague there, and then go to the ELSI issue related to the health disparity issue, which seems to me is something that the committee and everybody is in agreement with and that needs to really be addressed, but maybe in this section where you can make a stronger case for that, because that's something that came up in our group as well, is that we need to find a better place to put something like this.

So that would be my recommendation, because I think it's very confusing many times to use the proxy or the other terms that are being used. We ought to state it plainly that this is what the intent is, and I would recommend that.

DR. FITZGERALD: And we do have, as you know, in the third area, we have some of those. So we could drop the paragraph out here and make sure it's emphasized in the third.

DR. TELFAIR: Or refer to the recommendation. You can always say refer to the recommendation for the intent here, because I do think you do need to really address the intent.

DR. FITZGERALD: Right.

DR. TUCKSON: I would just like to emphasize where Joe is and take Francis' point. I think what we need to state is I think people are reading two different things here. So I think we ought to describe what your concern is. Francis I think teed it up very well, because you don't want to see a misuse. However, in the more positive activity, there needs to be the opportunity for research to do so and so. Nobody else knows that you're talking here about BiDil, so you need to declare what your anxiety is.

DR. FITZGERALD: Okay. We are a little late for our break, but let's do it right here, if that's okay with everybody. It's 11:00 now, and I think we're supposed to have a 15-minute break.

DR. TUCKSON: So if you're not here by 11:15, woe will befall you.

(Laughter.)

DR. TUCKSON: And we're going to have the cameras turned to your vacant spot so all of America will know you're not here.

(Laughter.)

(Recess.)

DR. TUCKSON: Thank you all for resuming on time. I mean to tell you, there are so few people with whom woe will befall. It's amazing.

Mr. Chairman, let's keep going.

DR. FITZGERALD: First of all, I just want to thank everybody for the comments and the insights. They are greatly appreciated. However, I did overstate the case a little bit earlier when I said this was our opportunity to sort of realign the universe and move stars around. The one thing I forgot to tell you is we can't mess with time; it just keeps going. So we have to keep going, and if we can be more succinct and targeted in our comments, that would also be greatly appreciated, but I do not wish to cut you off from making your comments.

So we're going to move on to gatekeepers. Now, again, it's important to understand here what we mean by this term. These were the groups that were identified as those that can enable, halt or redirect the course of pharmacogenomic technologies, and therefore they affect the integration and the patient access. We divided these entities into four groups: industry, the FDA, CMS and other third-party payers, and clinical practice guideline developers. Again, these were the ways that we broke it out. We thought that perhaps this was the most constructive way to do it, but we are willing to hear from you on that issue.

Looking at these groups, again the points of our discussion were are we covering the major issues, is there anything we're missing, and what are the high priorities. So looking at the role of industry, manufacturers' perceptions of risk and return on investment influence whether and how pharmacogenomic products are developed and marketed. So we talked before about incentives. There are disincentives to develop pharmacogenomic products. That can lead to a segmented market, which can lead to decreased profitability and can cause additional responsibility involved in coordinating co-developed products.

Then there's the role of the FDA. FDA approval affects manufacturing practices, conduct of clinical trials, market clearance, postmarketing surveillance, access to pharmacogenomic products and their use in clinical practice. That raises questions about the adequacy of genetic test regulation, which we will also get into this afternoon, so we don't have to solve all those issues here, the extent to which genetic data submissions will be required, premarket review of co-developed products, and labeling of pharmacogenomic products.

The role of CMS and other third-party payers. Ability to obtain coverage and favorable reimbursement critical to manufacturers' willingness to invest in R&D of new pharmacogenomic products, and the challenges here include the fact that Medicare does not cover preventive services, private plan coverage may be difficult to obtain, especially because of limited clinical

validity and utility information, reimbursement may not be adequate, and uncertainty about and variation in plans' evidence expectations.

Then we have the role of the clinical practice guideline developers. So the availability of practice guidelines affect the coverage of pharmacogenomic products and their uptake by health care providers, and evidence-based practice guidelines for pharmacogenomic products are indeed lacking.

So looking at this, are these the major issues? Have we missed anything? Are these the things of highest priority? I open it up to your comments. Remember, we haven't gotten into the recommendations yet. These are just the issues. Everybody seems all right. This is good. We like this brevity.

All right, let's look at the recommendations. Do they work as they are currently worded? Is there anything we're missing? Should some be deleted?

The first one. In looking at these recommendations, this is 6A, and this was flagged by the task force as being of higher priority. "CMS should clarify in writing that pharmacogenomics tests are diagnostic and thus eligible for Medicare coverage."

DR. ROLLINS: It is true that CMS looks at certain pharmacogenomic tests as being diagnostic in patients who have signs and symptoms of a particular disorder. CMS does not look at pharmacogenomic tests as being diagnostic in patients who do not have signs or symptoms of a particular disease. Again, going to the point of we don't cover preventive services, and for a person to have a predisposition for a specific genetic disorder, even though he or she may not have signs or symptoms of it, for that reason it would not be covered under that specific scenario. But as I said, if a patient did have signs and symptoms, then it would be covered.

I think this was one of the recommendations that was made before, that we made earlier, and I think currently the Secretary is looking at whether or not Congress can give us a designation for a prevention category. But at the current time, we don't have that.

DR. FITZGERALD: And if this were to stay as it is written, it would be supporting that change, that you would have a prevention category.

DR. ROLLINS: Correct.

DR. FITZGERALD: So then the question is do we want to support that change?

DR. FERREIRA-GONZALEZ: Could we make a recommendation to support that change so the underserved are being met?

DR. FITZGERALD: Pardon?

DR. FERREIRA-GONZALEZ: Could we make a recommendation to support that change?

DR. FITZGERALD: Well, this does I think, in essence, do that. Do you want to be more specific and say, for example, recommending that --

DR. ROLLINS: You could say, for example, in addition to covering patients who have signs and symptoms of a particular disorder, we're proposing that patients who have a predisposition for a

genetic disorder, even though they don't have signs and symptoms of it, the genetic test should be --

DR. FITZGERALD: And as I've just been informed, that would make us consistent with the coverage report that we've already sent along. But I think that specificity is fine to put in there.

Yes, Anand?

DR. PAREKH: And I think another way to say it, if James thinks this is acceptable, is differentiating between primary prevention and secondary prevention. In getting at the heart of the matter, it's primary prevention when individuals are asymptomatic, don't have the signs and symptoms and Medicare would not pay for it. But increasingly, for secondary prevention when there are signs and symptoms, Medicare would potentially pay for it.

DR. FITZGERALD: Francis?

DR. COLLINS: I guess I'm a little confused about signs and symptoms when we talk about pharmacogenomics. So if somebody comes in who has a diagnosis, they have signs and symptoms of an illness, they need a treatment, the treatment would be optimized if a pharmacogenomic test was first done to assess whether this is the right drug at the right dose, would that be currently considered acceptable under Medicare's definitions of when they will cover this kind of test?

DR. ROLLINS: Yes, because the patient would have signs and symptoms, or signs or symptoms, of the disorder.

DR. COLLINS: Okay. They wouldn't yet have signs and symptoms of an adverse drug reaction. You're not requiring that.

DR. ROLLINS: No.

DR. COLLINS: Okay, so that's good. But what this would say is that the earlier conversation we had about doing sort of prospective pharmacogenomic testing as, for instance, with G6PD and the military, would not be something that Medicare would currently cover. You'd have to come in with diagnosable signs and symptoms containing illness for which drug therapy is needed before Medicare would cover the cost of doing that pharmacogenomic test?

DR. ROLLINS: At the current time, that is correct.

DR. COLLINS: Well, obviously, I guess I would agree, then, if it's possible, to expand that universe of opportunities to the prospective one. That would be a good thing, and it is consistent with what SACGHS has previously recommended.

DR. FITZGERALD: Cynthia?

MS. BERRY: I don't know if we need a recommendation on this or not, but I know that CMS has employed the approach of least costly alternative, and in the area of pharmacogenomics perhaps that doesn't apply or it's more difficult to apply, because you can't just say here are two drugs that are comparable and we're going to pay for the cheapest one. There's a budget reason for that, and I'm not saying it's invalid, but as we drill down deeper and the science develops such that some people could not use the least costly alternative, perhaps there's room for at least acknowledging

it in the body of the report. I'm not certain that it rises to the level of a recommendation, but as long as we're at the CMS section, I thought I would bring it up. I'm not certain what our recommendation would be.

DR. FITZGERALD: But as far as this recommendation goes, that would still be in play even if we extend this recommendation to a preventive mode as well as a diagnostic one where signs and symptoms are already present. Is that correct?

MS. BERRY: Well, these are tests, and the other would be more once you've got the tests, what therapy would you use.

DR. FITZGERALD: Okay. Thank you. I think we'll definitely, following Jim's and Francis' comments, we'll make this more specific, and also make it clear that it's consistent with our earlier coverage report.

6B. "Health insurance plans should be more transparent in how they make coverage determinations for pharmacogenomic technologies by developing guidelines that define the type, quality and standard of evidence that must be met for pharmacogenomic technologies to be covered. Whenever a particular pharmacogenomic technology is denied coverage because it does not meet these evidentiary standards, health insurance plans should inform the test developer what additional evidence is needed."

Yes, Cynthia?

MS. BERRY: I'm the skunk at the party. I don't know if it goes here, and I think these recommendations are just fine. A question rises, and again, I don't know if it rises to the level of a recommendation or should just simply be touched on briefly in the report, and that is the impact of pharmacogenomics on the development and use of health plan formularies. Formularies are used in an aggressive way to help figure out what therapies are best, how can we manage costs, and this is something that is quite extensive in the private sector, and of course Medicare Advantage beneficiaries are subjected to that as well. There's a difficult tension between figuring out what drugs and therapies you're going to have on your formulary and reimburse for, and pharmacogenomics, because you may have a certain drug on your formulary and you'll pay for that, but some person could not benefit from that drug or therapy because of a particular genetic issue or marker.

So I'm wondering if it is worth considering a recommendation about when we have evidence like that, concrete evidence, not making that individual go through a rigorous appeals process, the standard thing that you have to do if you're going to go off formulary. I don't know what the recommendation would look like. I haven't thought enough about it.

DR. FITZGERALD: I don't want to jump to the next one before anyone else wants to comment, but the next one talks about addressing evidentiary gaps. That's pretty broad, but it sounds to me like in one sense you're addressing an evidentiary gap.

MS. BERRY: I'm saying when the evidence is out there already, how do we manage the tension between health plans' use of formularies and making sure that people have access to the therapies that they need that may not be on a formulary? We don't want to eliminate formularies, but we need to somehow reconcile the two.

DR. FITZGERALD: Reed?

DR. TUCKSON: I want to be careful here, because I'm from that industry, that I don't have a conflict, but the use of the word "more," they should be transparent, and that implies that they're not. I don't think that helps.

DR. FITZGERALD: Oh, I see, I see.

DR. TUCKSON: A small point.

DR. FITZGERALD: We're just trying to get all the flaws out of the glass, that's all.

But thank you, Cynthia, on that. Do you think we need a recommendation directly to that, a formulary recommendation?

MS. BERRY: If I had one I would blurt it out, and I don't, but I think at a minimum it should be acknowledged briefly in the report.

DR. FITZGERALD: As an issue that certainly needs to be --

MS. BERRY: But perhaps someone else has an idea. That's why I just wanted to raise it.

DR. FITZGERALD: If you do later, you can always drop us a line.

Okay, 6C. "HHS should provide resources to relevant agencies to address evidentiary gaps identified by health insurance plans."

Reed?

DR. TUCKSON: I don't want to be the skunk at the party here either.

DR. FITZGERALD: We're getting so many that it doesn't much matter.

(Laughter.)

DR. TUCKSON: To say that the Secretary should provide resources to fill evidentiary gaps, I mean the budgeting process and the prioritization -- we're getting ready to come back with a large pop study -- I mean, there's a lot of stuff on the plate here. I think it's kind of tough to make a serious recommendation that HHS should provide resources. It's pretty definitive here that we're saying this is more important than some other things. I'm not sure how to handle this.

DR. FITZGERALD: Anand?

DR. PAREKH: Off of Reed's point, and maybe Dr. Downing can comment as well, I'm not sure if this recommendation went forward, if the Secretary's office would know what to do with it. Maybe it's just kind of a statement here and there's more in the briefing packet, but it's a bit broad and vague.

DR. FITZGERALD: I'm just making sure that it's the same as it is in here. Okay, this is exactly how it's in our text.

Emily?

DR. WINN-DEEN: I guess the problem I have with it is, as much as from a manufacturer's point of view I'd like to say this is all on HHS' shoulders, I don't think it really is. I mean, I think there's an obligation from both parties, the manufacturers, drugs and devices, to play a part in closing the gap of evidence so that a test can move into normal clinical practice, and it's not just an HHS activity.

DR. FITZGERALD: So would you want to delete or rewrite?

DR. WINN-DEEN: Well, I don't know. I'm not in the delete mode, but I think you need to definitely say to encourage public/private partnerships or something in there.

DR. EVANS: I'm in the delete mode. I think this is so broad as to be meaningless, frankly.

DR. FITZGERALD: All right. But you don't have any specification to give to it which would make it meaningful?

DR. EVANS: No.

DR. FITZGERALD: Scott?

DR. McLEAN: I just want to go back for a second to B. Different health insurance plans will have to make a judgment call on standards of evidence and whether or not something merits inclusion in their services. So there may well be that different insurance plans will have different interpretations of this and offer different pharmacogenomic coverage. That's going to be a marketplace issue, and then the consumers will go out there and say I like this insurance company because it provides me with these services. Is that the intent of putting the burden on the insurance plans to make that judgment?

DR. FITZGERALD: To at least be transparent about what they're doing?

DR. McLEAN: Sure, or to even be in that role in the first place. So each insurance plan will then have to have internal expertise on making judgments about pharmacogenomics, right?

DR. TUCKSON: Well, I think this takes us back to the general conversation about genetic exceptionalism and so forth. At the end of the day, all health plans follow a pretty rigorous and a pretty standard way of viewing the evidence for any of these new things. A lot of it is based on CMS guidance, first of all, so CMS is enormously important in this, and then we all have various ways of doing it. So I don't think that there will be any super-special thing about pharmacogenomics per se. It's just simply is it in the peer-reviewed literature, is it evidence based, et cetera, and then what is the stuff that Cynthia and Debra commented on in terms of the availability of cost effectiveness kinds of information so you can do the pharmacogenomics and so forth.

So my point is, Scott, in trying to be responsive to you here, that this will be handled the way that everything else is handled. The challenge then becomes having appropriate research and literature assessment available.

DR. FITZGERALD: Okay, thank you.

Gurvaneet, is this on 6C?

DR. RANDHAWA: Yes. I'm wondering if this is not overlapping with 11B, which is also talking about resources and coordination done by the HHS. To me it seems to be speaking to the same issue.

DR. FITZGERALD: Okay. My sense with this is we may have hit a delete for the most part on this, because it is rather broad. So, everybody, is that the general feeling? Okay, I don't see anybody dying in this trench, so we'll let that one go and on to the next.

Again, the next part here is the implementation section, and this is taking the information that is developed in research and gone through the gatekeepers and putting this out into clinical practice. This would involve education and guidance, information technology and pharmacogenomics, economic implications, ethical/legal/social issues, and the coordination of HHS activities. So again, which are the major issues? Are these adequate, and should we get rid of some? Which we've actually done now.

So provider education and guidance. Genetics education and training by health professionals, payers, regulators is insufficient. Limited information is available via labeling and practice guidelines about how to interpret pharmacogenetic test results and how to use them to inform treatment decisions.

These are the issues. Genetics education is needed to help consumers make informed treatment decisions. Direct access to pharmacogenetic testing via over-the-counter sales or direct-to-consumer marketing may increase inappropriate use of these tests. This could lead to increased health care costs, potential for misinterpretation of test results, misinformed health decisionmaking, and adverse health consequences. The uptake of electronic health records is still in its early stages and there's no consensus yet on how genetic information should be stored in these records and who should have access to the stored data. Obviously, lack of harmonized standards for storing and exchanging genomic data, and need for pharmacogenomic decision support tools and reminder systems.

Economic implications. The use of these technologies will likely add to health care costs, at least in the short term. Need to examine the benefits and costs of investment in these technologies, and there's little research -- we've heard this before -- on the cost effectiveness of pharmacogenomics interventions.

What are some of the ELSI issues that we haven't raised yet? Financial barriers to pharmacogenomic products, although that has been raised now; high co-pays under insurance and no insurance can result in access disparities; concerns about genetic discrimination, which we talked about a little bit; and liability risk if the provider fails to administer recommended tests.

In the coordination area there are lots of activities that are ongoing. We have a list in Appendix A. There may be more there, but as you can see it's already an extensive list, 23 pages, and yet there's no single coordinated framework or action plan to address pharmacogenomic challenges or share information about activities among the federal agencies.

These are the issues that we have highlighted. Is everybody good with these issues? Is there anything that we've missed? Is there anything that you think is inappropriately highlighted?

DR. LONG: May I just comment?

DR. FITZGERALD: Sure.

DR. LONG: I do think there are some activities on behalf of professional organizations, professional medical organizations and coalitions among organizations. So Slide 65 sort of dismisses everything as insufficient. I mean, there are nascent activities going on to educate practicing physicians, to incorporate it into medical curricula, among genetic counselors, among human genetics testing groups. So it's a little bit all dismissed.

DR. FITZGERALD: Well, the intent there is not to dismiss anything. The intent is to acknowledge that even in spite of what's being done, as you mentioned, sort of in a nascent way, is not sufficient. We don't want to stop here. We don't want to say that where we are is a good place.

DR. LONG: Nascent is what I'm thinking.

DR. FITZGERALD: How about if we say "is currently insufficient"? Is that okay?

DR. LONG: Yes.

DR. FITZGERALD: We don't want to downplay anything, because everything that's going on now is certainly needed, but we need more.

Yes, Francis?

DR. COLLINS: Again, just a fine nuanced point here. In Slide 68, this implication that pharmacogenomics will add to health care costs, well, maybe not if what you do is reduce the incidence of adverse drug reactions, which cost a huge amount both in terms of health care economics and in terms of human suffering. So maybe that's a little too strongly worded there, as if it's a definite uptick in the overall expenses of the medical care system. I would argue that really ought not to be the case.

DR. FITZGERALD: Well, we do have the word "likely" in there. The question is if you had to make a guess which way it was going to go, which way do you think it's going to go?

DR. COLLINS: I don't know.

DR. FITZGERALD: Debra?

DR. LEONARD: But what you could say is that pharmacogenetic technologies are an additional cost to the health care system, or the use of pharmacogenetics is a new development in the health care system, and then the need to examine the benefits and costs of investment or use of pharmacogenetic technologies is your second bullet. It's new, so it's not something that's currently being done. But in the balance, the second point is the question of is it going to be cost effective and save on length of stay or adverse reactions such that the cost of a $300 test outweighs the savings.

DR. FITZGERALD: Well, again, remember that these are issues and not recommendations. So what we're doing is raising these as issues, and in the discussion, where we look at the economic implications, we do in a sense -- this is bulleting what's in here, and let me just read that. "The rapidly increasing cost of health care is a major concern in the United States. Technological innovation is among the most important drivers of those costs," which, just as you mentioned, it is a new technology. "While new technologies may improve the length and quality of life or be cost effective, they almost invariably increase total costs."

DR. EVANS: But I think that Francis' point is right. I think there should be an acknowledgement in this first bullet that they may add to health care costs, but on the other hand may actually reduce costs, which is different from cost effectiveness. Cost effectiveness says it's worth the money. It is conceivable that pharmacogenomics will save money.

DR. COLLINS: That analysis has already been done for warfarin. If you incorporated right now, based on what we know, just P450 and BKRC1 testing, you would save money overall for the health care system because of all those adverse events that you would have predicted and prevented.

DR. FERREIRA-GONZALEZ: Taking up that point, when you look at infectious disease, when we introduced HPV testing for Pap smears, you increase the cost of taking care of that particular patient, but the overall cost of the health care has been significantly reduced. So maybe that's how we can phrase it, that maybe we're adding a test to that patient, but the overall cost will be significant savings.

DR. FITZGERALD: Right.

Cynthia?

MS. BERRY: Another thing that we should factor in, and I think we could craft a recommendation on this, but in the real world application we understand the cost savings overall downstream. Federal programs have to pay attention to what the Congressional Budget Office would say. So any changes, legislative changes in federal program coverage and other statutory changes are all going to be dependent on whether CBO decides there are cost savings or not, and traditionally CBO does not recognize downstream savings or avoiding hospitalizations or avoiding adverse drug events. They simply say what's the cost of the therapy, how many people would benefit from the therapy, multiply that and then add in a few additional numbers for the woodwork effect, and suddenly that's the cost. It's frustrating to everybody in health policy because we know that in the real world we can achieve savings, but in the world that federal programs have to pay attention to, they can't get CBO to acknowledge those savings. If there's some way we can craft a recommendation, whether it's pushing for some form of dynamic scoring, or if that's a bad word call it something else, that would push CBO to at least consider these types of data that would help make the case and that would lead to enhanced coverage, at least in federal programs. But it's a real problem that we face.

DR. EVANS: I think that would be a tremendously important idea. I didn't realize that about CBO's perspective, which seems unbelievably limited, and maybe that should be a separate recommendation, take out that first bullet and say something like pharmacogenomics may increase costs but ultimately, in an overall sense, may decrease costs, and add something about how CBO's perspective should --

DR. FITZGERALD: Just for this issue, if everybody would look -- it's on page 9 of your executive summary. Number 9 is the economic value of pharmacogenomics, and that is another recommendation that we are going to come to. We do seem to be getting a little bit of an overlap here, so one way to deal with that would be to either change this first bullet and deal with the issue in 9, deal with it here -- I mean, we have to just figure out where we want to go with this. We could in this one -- the first bullet could say, "Currently there is concern that the use of PGx technologies will likely add to health care costs" or "may add to health care costs." We could do it that way, "there is concern."

DR. COLLINS: Or you could just drop the first bullet.

DR. FITZGERALD: And pick it up in 9, right.

Emily?

DR. WINN-DEEN: I'm just a little confused because these are not the recommendations we're looking at here. These are just summaries of what's in the text.

DR. FITZGERALD: Number 9 is where we pick it up. That's right. These are the issues that we're talking about here, and that goes to 9. I'm sorry.

DR. COLLINS: But let me then argue that the text you read us needs some tweaking because it overstates that we know what the consequence is going to be in a very negative way.

DR. FITZGERALD: Right. So the reality is there is concern. I think we can say that. I mean, that empirically we can say in these issues.

Yes, sir, Michael?

DR. AMOS: I think that what everybody is kind of worried about is that somebody will look at this one statement and take it to several orders of magnitude higher than it really means, and by taking it out or recrafting --

DR. FITZGERALD: They can't see this statement. This is an issue that's in the report. But you're right, we can rework that part of the report that I did read.

DR. AMOS: But the critical piece is, yes, it's going to cost a lot of money to develop these technologies, but the goal is to lower health care costs.

DR. FITZGERALD: Understandable, understandable. We can go back, Francis, in that section and rework that.

Any other issues that we covered that are raising red flags? No? Okay, then let's get to the recommendations, 7A.

DR. HANS: I actually had one point.

DR. FITZGERALD: Sure.

DR. HANS: I'm a broken record on this point, for those who are in the other work group. The last point is an argument that can be made for NIH's entire budget, and I hate once again to create an exceptional argument for this area of technology and would hope that the discussion in the report acknowledges that this is not specific for this technology or this application. It is overall for all medical technology, so it's not exceptionalized in any way.

DR. FITZGERALD: Oh, I see. Okay, good point. To be honest, I'm not quite sure how that comes out in the report, but I'll go back and look at that and make sure that that's also not the case.

In 7A, again this was flagged by the task force as a high priority. "As evidence of clinical validity and utility for a pharmacogenomics technology accrues, HHS should support the preparation of meta-analyses and technology assessments summarizing the evidence base. These analyses and assessments should be disseminated to professional organizations to facilitate their development of clinical practice guidelines," which gets back to something Rochelle mentioned earlier about the way people are trying to get up to speed on this.

Anybody have a comment?

DR. ROLLINS: You see a lot of meta-analysis looking at randomized clinical trials, as well as meta-analysis looking at cohort and case-control studies. It's extremely rare that you find meta-analysis of diagnostic studies simply because of the receiver operator characteristics, as well as the changing endpoints. I'd suggest instead of using the word "meta-analysis" you might want to use the words "systematic reviews," which a meta-analysis is, and you can say "systematic reviews looking at how test results were used in the management of patients," or something like that, again reiterating the word "management," but taking out the word "meta-analysis" and using "systematic reviews."

DR. FITZGERALD: "Systematic reviews," which is a broader term, which should be including meta-analyses and others. That's reasonable. All right, good. Thank you.

7B. "HHS agencies should collaborate with federal, state and private organizations to develop, catalog and disseminate case studies and practice models in the use of pharmacogenomics technologies."

Anybody? Everybody's good with that? All right.

7C. "HHS should provide resources to professional organizations that will help enable their membership to meet established competencies on the appropriate use of these technologies," again trying to facilitate what's already ongoing, which we judge to be a good thing.

Yes, Michael?

DR. AMOS: I'm sorry. Just on B, the drug companies and diagnostic companies do a lot of this as far as working with physicians and laboratories, reference laboratories in trying to teach them how to use their products. So maybe industry would be included in this. Because we've asked industry to do a lot, maybe we can help industry.

DR. FITZGERALD: So you would say here "should collaborate with federal, state, industry and private organizations."

DR. AMOS: When you say "private organizations," does that include industry?

DR. FITZGERALD: Yes, I think.

DR. AMOS: Okay.

DR. FITZGERALD: But do you think we need to emphasize it? That's my question.

DR. AMOS: If it's included, then everybody's comfortable with that. That's fine.

DR. FITZGERALD: Good. And then C was providing resources to professional organizations. We're good with that.

I'm sorry. Cynthia is not.

MS. BERRY: C1 maybe. I throw this out to the group to find out if you think that there's a certain element of reporting that we would want to ask providers to engage in. What I'm trying to do is think about if there's a way to weave pay for performance, weave pharmacogenomics into the pay for performance concept that HHS might be moving towards, which is to incentivize physicians and other providers by paying them a little bit more to do certain things, and down the road the idea would be for quality measures. But initially, I think it will start out as reporting. So if they report certain data in, they will get enhanced Medicare reimbursement. Is there some recommendation that we can talk about, or is it all too preliminary, that would weave in reporting of data, what kind of data that could be incorporated in the pay for performance approach? I don't know if the science is still too new and we're not there yet, but if there is data that physicians would have that would be useful, if we would incentivize them to report that data somewhere, and then that could be woven into the pay for performance approach.

PARTICIPANT: We have to make sure they're covered first.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think this is, Cynthia, right down the middle of the plate for what we started the meeting off with when Sheila was here regarding the America's Health Information Community and so forth. So this is the essence of what that's all trying to do, to find a way to connect the information around clinical practice that derives from a physician's office records and elevate that up in a more convenient way to larger activities. So I think we should try to find a way to connect that into the AHIC activity. I think that's the way you sort of get at that.

As regards the specific thing here, I'm still struggling with this one. I think that if we're saying that HHS should work with professional societies to facilitate the continuing professional development of their members, that's fine to me. But the idea that the government is somehow or another going to write a check to professional societies to help them do a better job in this area, then you get the radiology imaging committee comes forward and says, all right, where's my check for that, and it goes on and on and on and gets absurd.

At the end of the day, this is what professional societies do. That's what they're supposed to be doing. So the idea that the government is going to subsidize those societies to do this, clearly there must be some things that we can all do to help them to do their job. So we'd be working with them to facilitate the continuing professional development of the physician. That seems reasonable.

DR. FITZGERALD: Right. So right there, you're saying that using the words "provide resources," everybody is going to just think money instead of resources, which is broader than just money. Okay, good point.

Joe?

DR. TELFAIR: I was just thinking not too different than what Reed just said, and that's because I don't know if this exists already. But efforts at either providing a mechanism for coordination or to coordinate, help and assist organizations in coordinating the effort there, because that would

mean that you have a cross-organizational or even a collaborative, if you will, group that has representation from a number of organizations that will probably continue to work on what they're working on but that would have a number of things built in, which is the transparency issue that we need to talk about, the accountability issues that will be there, as well as having up to date, real-time assessments of the efforts that are going on.

So that's what I'm recommending, that instead of saying resources, saying coordination, provide a mechanism for coordination or facilitate coordination, whatever way you want to put it, but the idea would be that we would make a recommendation, and this may be something that's already there that just needs to be tweaked a bit that would be almost cost efficient on that, essentially. That's along the lines of what Reed was saying, but I was just thinking when I read this that that would actually be a better thing than that.

DR. FITZGERALD: Reed?

DR. TUCKSON: I think that's terrific. To nuance my comment, on the one hand I am legitimately concerned that HHS would be sending public money that's in short supply to the societies to accomplish this. On the other hand, the societies get very freaked out if government is going to try to coordinate their efforts to tell them how to practice medicine. So I think the idea of facilitating a rational effort where people are trying to work together, but the government certainly shouldn't try to coordinate medical societies in terms of how they're going to practice their profession. I mean, that's their expertise, but they need to be supported.

So I think the way you phrased it was good. I just realized I needed to give the other half of that balance/nuance here.

DR. FITZGERALD: Okay. So what do we have right now? How about "to facilitate the ongoing professional development of their membership that will enable their membership to meet established competencies"?

DR. EVANS: Again, can't we just say "work with," to "work with professional organizations"? Because you sure don't want to imply, like Reed says, that the government is going to be coordinating. Facilitating could also mean giving money.

DR. FITZGERALD: I like "work with."

DR. TELFAIR: I understand the facilitation part being difficult, because it is sort of what to do, but it seems to me that there are models that already exist around other things. I guess my point is that whatever way the wording comes out, it really needs to be a joint collaborative effort with the HHS and professional organizations.

DR. FITZGERALD: What we could do is we could say "HHS should work with," and then say "along the lines of," and if you could give us the examples of those models -- you don't have to do it now -- we could use those as an example, and that way you give an idea of how we should go. That's 7B.

DR. AMOS: So once again, industry has a lot of activity in this area in educating their customers.

DR. FITZGERALD: Right. We could use those models, right?

DR. AMOS: Well, I think what you want is some universal resources, some database or teaching tool that everyone can use, not just the professional societies, that would help industry as well to do what they do, because there's a significant activity that industry undertakes in working with their customers.

DR. FITZGERALD: So we're back in 7B again?

DR. AMOS: No, I think it's for both. I mean, you say professional organizations, but I think it's industry as well.

DR. FITZGERALD: So you're saying "HHS should work with professional organizations and industry." But how does that help enable their membership meet established competencies?

DR. AMOS: Well, you'd have to change it a little bit, but I think the role of industry in educating their customers and making the resource available to industry, the goal is to improve health care, and industry plays a large part in the teaching.

DR. FITZGERALD: Right. I'm just trying to make sure we don't have that somewhere else down the road here, which we might. We'll flag industry, and then we'll see if we've got it anywhere else down the road.

Anybody else?

DR. HANS: I have a few concerns, actually, about that last suggestion. The motivations of industry for providing information to practitioners, there are a variety of motivations in that. I would want the subcommittee to examine all the aspects of that suggestion. I would just say that the VA has published two reports on this issue through the National Center for Ethics in Health Care, the National Ethics Committee.

DR. FITZGERALD: Okay. Thank you.

7D was one which, again, the task force flagged. "FDA should continue to work with drug and diagnostic manufacturers to provide adequate labeling information so that clinicians can make dosing decisions based on pharmacogenomic test results. The labeling should clearly describe the test's analytic and clinical validity, and provide dosing guidelines based on test results." So we got the analytic in here anyway.

DR. LONG: I was thinking of saying you might not want to box yourself into dosing decisions, just decisions. At some time a test is going to come out which tells you which drug to use. Twice you refer to dosing, and you could just eliminate that.

DR. FITZGERALD: Okay, that clinicians can make decisions based on that. Right, okay.

DR. EVANS: As somebody who encounters a lot of confusion among clinicians about how to use these things, it may sound trivial but I would put specific guidelines based on test results. In other words, physicians are very unfamiliar with these types of things and are going to need very specific guidance. I think we should emphasize that.

DR. FITZGERALD: Okay. So we'll take out "dosing" and put in "specific."

DR. LEONARD: You may want to say "specific guidelines" or "recommendations" or whatever, such as dosing or drug selection.

DR. FITZGERALD: Okay, good.

DR. MANSFIELD: To slice this even finer, I think you might want to say which label you're talking about. The diagnostic label already has analytical and clinical validity usually of the test, but the drug label does not, as far as I'm aware. So you might want to point towards which label you're talking about.

DR. FITZGERALD: So instead of saying both drug and diagnostic?

DR. WINN-DEEN: I think we discussed this at the task force, and I don't know why the change didn't get made. But the drug labeling provides the dosing kind of information, and the diagnostic is the one that should have the performance characteristics.

DR. FERREIRA-GONZALEZ: Yes, because, for instance, you can do genotyping 2G6, which is going to be used for many different drugs.

DR. WINN-DEEN: Right. So we need to just clarify which parts of that are for the diagnostics and which are for the drugs.

DR. FITZGERALD: So what you want to do is tie drug to dosing and diagnostic to selection?

DR. WINN-DEEN: Well, diagnostic is the thing that's going to have all the analytical characteristics that you're talking about, analytical and clinical validity.

DR. FITZGERALD: So everybody is comfortable with the general thrust of this. How about, Emily, if we rework that a little bit?

DR. WINN-DEEN: Sure.

DR. FITZGERALD: Okay, good. And we'll put in those other suggestions at the end about what Debra was talking about.

Okay, 7E. "FDA and NIH should continue their efforts to provide up to date, real-time prescription drug label/package insert information. The Internet-based DailyMed project currently underway will be wide-reaching, but to ensure that all sectors of the public have access to this information, these agencies should develop other ways to reach members of the public who may not have or use Internet access." Okay? Good.

7F. "The Office of National Coordinator for Health Information Technology should promote the incorporation of pharmacogenomic test information into electronic health records, as well as decision support systems and tools that can notify providers about pharmacogenomic test and labeling information that could help them make appropriate treatment and dosing decisions." Okay? Good. Great. Thank you.

7G. "Until the electronic health record becomes a universal feature of the health care delivery system, HHS should identify other ways to make best pharmacogenomic practices more readily available to health providers." This may also add, Reed, to the "working with professional organizations." All right, great.

Now information for the public. "HHS should fund studies of public awareness of the benefits, risks and limitations of pharmacogenomic technologies," and I think this got to an earlier issue we were talking about, hype versus what's the reality, where are we with the technology. So this would be part of that. Everybody is on board. Great.

8B, again one flagged by the task force. "HHS should ensure that educational resources are widely available through federal websites and other appropriate media to inform decisions about the use of pharmacogenomic technologies." This is just public awareness. Good.

8C. "HHS should dedicate resources to public consultation activities to gauge the public's receptiveness to and concerns about these technologies and their willingness to participate in clinical research studies involving pharmacogenomics." Here I do believe resources would include funding.

Joe?

DR. TELFAIR: Just a question of clarification, and maybe this is for your group. The issue of literacy, health literacy, in terms of the use of public education, I'm assuming that that was something that was taken into account in terms of how information is given out, level of understanding, because this one is related. I mean, I was waiting for this. So it does make a difference if it's understood before you can actually comment.

DR. FITZGERALD: Right, right. My understanding is literacy would be involved across the board. In the projects that have been done so far, and maybe Francis can tell us what the situation is currently with their consultation, but I do believe in some of the things that have been done that was taken into consideration, how to engage the people who were at these meetings that were held to get public engagement.

DR. COLLINS: That set of meetings is primarily focused on the question of large-scale population cohort studies. So to the extent that you can map across those reactions into this area, there might be some information to be gleaned there, but it's certainly not asking the specific questions --

DR. FITZGERALD: No, but is literacy an issue that's taken into consideration when you're addressing that?

DR. COLLINS: Yes.

DR. FITZGERALD: Right. I think it is across the board. Thanks.

Cindy?

MS. BERRY: I was wondering if we might consider deleting 8A because I'd go out on a limb to say that there's very little public awareness. I don't know that HHS needs to fund a study about public awareness. My guess is they probably don't know anything and we should just move right into assuming that they don't know what they need to know and that they should provide resources to help educate the public.

DR. FITZGERALD: Hang on one second. Just let me make sure here that this is accurate. I think this was preliminary to 8C, but you're right, if you're doing public consultation you're presumably going to find out what the public knows and doesn't know. But in any case, yes.

Joe?

DR. TELFAIR: What I would actually suggest is that under HHS, if you look at what's going on in HRSA, which is focused on access, if you look at what's there, there are projects past, current, and in process related to this issue of public awareness. Maybe the recommendation would be that they use existing mechanisms to enhance, instead of just assuming that they don't exist. So I would focus on that. Again, it's using what's already there and just tapping into that to use for this purpose.

DR. FITZGERALD: So we could just say HHS should continue to fund studies, and then cite the ones that you mentioned, such as, et cetera.

DR. TELFAIR: They already have in place the commitment to fund these. It's not studies but it's awareness projects.

DR. FITZGERALD: Oh, that's the education piece then. I think we have three levels, and I'm just wondering if we need three. We have awareness, education, and then public consultation. So are we saying that we can fold 8A into 8C? Is that the general sense here? We could always just say awareness and consultation? Okay. Then that would help because we can get rid of one. All right, then we'll do that, fold 8A into 8C.

Reed?

DR. TUCKSON: Just one point of order as you continue to go through this. I'm trying to see if we can find Greg to just comment. They're going to look for him. I think it's important to connect this, at least one recommendation, if the committee is willing, to whatever it is that this personalized health agenda is that HHS is already doing. Is that in a different section? Because if it is, I don't want to be redundant. But I think HHS has pretty well telegraphed to us where they're going to spend their money and where their energy is. So I think that if you know there's a train leaving the station with lots of gas in it, you might want to jump on board that train. Anything else is sort of listening as the train goes by.

DR. FITZGERALD: Right, and I think in our discussions with Greg, this is one of the reasons we tried to pick some for higher priority rather than lower, because this is where the Secretary's personalized medicine initiative was already.

DR. TUCKSON: So that helps me, then, that you're putting it there because you know that there's a train. What I'm saying is you might want to say I'm going to catch the 3:09 outbound to Philadelphia.

DR. FITZGERALD: Well, we know there's a light at the end of the tunnel. This time we're hoping it's a train.

(Laughter.)

DR. LONG: May I follow up on that, too? It's an observation again, reflecting back on Slide 80. It's referring to electronic --

DR. FITZGERALD: I'm sorry?

DR. LONG: 80, 7G. It's referring to electronic health records, as though they're universal, and they're not right now.

DR. FITZGERALD: No, it says "until."

DR. LONG: Right now, for example, in HMOs there are a lot of electronic health records, but they're different from organization to organization, and I think I'm reflecting on what you're saying, that one of the goals here is getting things uniform so you can do studies across groups.

DR. FITZGERALD: That's one, right.

DR. LONG: And you might need to be more --

DR. FITZGERALD: In the interim, we want to do this, okay? So we do have a thing where we say we need to put those databases together, absolutely, and they've got to talk to one another, absolutely. In the meantime, we've got to also continue to not let this fall through the cracks.

Yes, Joe?

DR. TELFAIR: Just a model that you recommend is what already exists in state genetic health plans, what is part of the list of things that state genetic health plans should be working on. This comes out of HRSA, MCHB. Just a point of reference.

DR. FITZGERALD: Okay. This is for which one?

DR. TELFAIR: For the recommendation I was making earlier in relationship to --

DR. FITZGERALD: Educational resources?

DR. TELFAIR: Yes. Since A and C are going to be combined --

DR. FITZGERALD: Okay, great. Thank you.

Then there was a comment back here. Do you have a microphone back there somewhere? Oh, okay, you got it. I think it has to come on. Go ahead, just try it.

DR. MITTMAN: I'm Dr. Ilana Suez Mittman, and I'm with the Maryland Office of Minorities and Health Disparities. I would try not to merge. I really like 8A through C as they are, and I think that there is a very important distinction between education and awareness of the public, engaging perceptions of all groups about this technology and their desires and needs and how those can be met. So I would try not to combine or merge any of those initiatives as they're individually distinctive, I think.

DR. FITZGERALD: Okay.

Yes, Barbara?

DR. McGRATH: I think that's terrific. Maybe what I would do is build on that and talk about -- I'm going back and forth here. I agree that we don't necessarily need studies on awareness, but we definitely do on perceptions and opinions and beliefs. So maybe using that specific language

of perceptions rather than awareness would keep it clear, separate from awareness. Does that make sense?

DR. FITZGERALD: Okay. So you're saying for 8A, "HHS should fund studies of public perceptions and beliefs of the benefits, risks and limitations of pharmacogenomic technologies." Is that correct?

DR. McGRATH: I'm by nature a deleter, so in C I would put the words "public perception" in there.

DR. FITZGERALD: Oh, got it, to gauge the public's receptiveness to. Okay, thank you.

We're jumping around just a little, but I think we're good with 8. Is that correct?

Now we're on to 9. This was, again, one that was flagged by the task force and something important since it's come up several times, about the economic value of pharmacogenomics. "HHS should determine the economic value of investments in pharmacogenomic research and development relative to investments in other health and non-health-related areas. This assessment should analyze the effects on society as a whole, as well as each individual stakeholder." This goes back to that discussion we were having before. Is it going to affect an individual? How is it going to affect society? How does it fit into the whole larger picture?

Debra?

DR. LEONARD: I'm just concerned by the emphasis on the economic value of the research and development, as opposed to the use of pharmacogenomic technologies.

DR. FITZGERALD: Okay. I think we could easily put that in, research, development and use.

DR. LEONARD: Well, do you want to assess the economic value of the research and development? The Secretary has already come and said that he's investing in this. This is a high priority. I mean, are we going back and asking him to assess the first three research and development recommendations to say the cost effectiveness of those or the value of those, or are we talking about really the clinical use of pharmacogenetics, which is the part that's here? I mean, that's the part we're in, the section of the recommendations we're in.

DR. FITZGERALD: Right, right.

DR. LEONARD: The clinical use of these.

DR. FITZGERALD: My sense was, if I remember correctly from our meeting, that it was difficult to tease these all apart. I mean, I think use was supposed to be in here anyway. It was sort of implied, although you're right, it should be put in there specifically.

DR. LEONARD: But couldn't it just be reworded that HHS should determine the economic value of pharmacogenetics relative to investments in other --

DR. FITZGERALD: Right, we could just put "investments in pharmacogenetics relative to investments," right, and not run into that problem.

DR. EVANS: It seems to me in this area might be the most appropriate place for the previous discussion, like what Cynthia brought up, explicitly saying that pharmacogenomics does hold the possibility of lowering health care costs and that this should be looked at in some kind of global sense in not in a limited sense, so that we encourage the CBO to --

DR. FITZGERALD: I think this is what we have in that second paragraph.

DR. EVANS: But I think it should be more explicit.

DR. FITZGERALD: Okay. So the effects on society as a whole as well as each individual stakeholder. Why don't you write it out?

DR. EVANS: Okay.

DR. FITZGERALD: Now, do we need the CBO example?

MS. GOODWIN: That's only for legislation.

DR. FITZGERALD: That's kind of legislative limited, right.

MS. BERRY: Well, it is. So it pertains to federal programs. The private sector is not bound by what CBO does, but it's also an awkward, unrealistic world, CBO, but it's something that we have to face. So I think it probably needs its own little recommendation.

DR. FITZGERALD: Recommendation, or just put it in the report?

MS. BERRY: Well, start out by putting it into the report. Now, if we're going to weave it into this same recommendation, we could maybe direct HHS to drill down a little bit more into the types of data that CBO might be receptive to examining. Maybe we can get at CBO indirectly that way and not have a new recommendation but amend this current one.

DR. FITZGERALD: Could you write up a possibility for that? Okay. I think it could fit in sort of like "such as looking at this particular issue."

DR. FERREIRA-GONZALEZ: I'm just trying to figure out that we don't lose some of the points that Debra was trying to make earlier about outcomes research and will we allow for funding for investigators to look at the economic benefits or the impact on the whole health care. So have we covered that in the first part of research and development, or should we add in this economic value that maybe HHS should fund some of this kind of research?

DR. FITZGERALD: Well, I think what we decided here anyway was to drop -- we would just say "the economic value of investments in pharmacogenetics relative to investments in others." Is that okay? Because it's inclusive.

DR. FERREIRA-GONZALEZ: Determining the economic value, will that provide funding for investigators to do outcomes research? Is that part of that?

DR. LEONARD: That was added back in the other research and development recommendations, I think.

DR. FITZGERALD: Oh, back in the first section? We're looking at that right now. As we look at that, anything else on 9?

Okay, we move to 10, ELSI research. "NIH should fund more research on the ethical, legal and social implications of pharmacogenomics. Gaps in current knowledge include questions about whether integration of pharmacogenomics into clinical and public health knowledge will exacerbate health and health care disparities, limit access to or decrease the quality of health care, increase medical liability, or result in genetic discrimination. Steps should be taken by HHS to address any problems identified through this research."

Does this capture it? Francis?

DR. COLLINS: Just the notion that we are, after all, in a zero sum at the present time as far as NIH budget. So if you say more research, the implication there is that you will do less research of something else. If that's what you mean, then okay, say it. But if what you really mean is that NIH should continue to encourage research on the ethical, legal and social implications of pharmacogenomics, that might be a little easier to fold into all of the other ELSI needs that are out there, because there are plenty of them.

DR. LONG: I also endorse encouraging high-quality applications, and they will get funded through the present system, rather than needing to start a new program.

DR. FITZGERALD: Absolutely. I hope we weren't necessarily implying starting a new program. But what's the level of funding right now?

DR. COLLINS: For pharmacogenomics research?

DR. FITZGERALD: For ELSI.

DR. COLLINS: Oh. For ELSI, it's about $20 million a year.

DR. FITZGERALD: And what's the percentage? Do you know?

DR. COLLINS: It's 5 percent of the NHGRI budget, and there's ELSI research going on in other institutes as well that's not captured in that number.

DR. FITZGERALD: Right. So we should say "continue to fund." "To ensure"?

DR. COLLINS: Or encourage.

DR. FITZGERALD: "Encourage funding." But we have funding.

DR. LONG: We need to encourage people to apply the high-quality applications. It's promote, encourage, help, assist, development of.

DR. FITZGERALD: Joe?

DR. TELFAIR: I think I'm going to add something, actually, to what's being said, because the reality is that you have more than one mechanism within DHHS that's looking at these issues, and it seems to me that it's a very straightforward process, something that actually was done not too long ago by Francis' shop, which is to do some work looking across agencies and programs that

already exist to collaborate on high-quality research in this area, because you're supporting an effort that exists and you're just reinforcing an effort that exists and you're not adding anything to that beyond having them just reinforce, which is a good thing, what is already there and should continue, which is cross-cutting.

DR. FITZGERALD: Right. Now, my question is does that fall under the next recommendation, which is trying to coordinate all the HHS pharmacogenomics activities, which I presume would include ELSI? I don't want to duplicate recommendations if we don't have to. I'm presuming that includes ELSI, if that's okay. Or do you think we need to emphasize this? What we could do in that one is give an example such as the ELSI endeavors that are ongoing at various institutions, something like that.

DR. TELFAIR: I just think that if you're going to make a recommendation such as this, given the current environment, given what we anticipate to be the environment for a bit, we need to make recommendations that are going to be looked at as being realistic. That's all I'm really saying. So I'll leave it up to you to decide.

To me, the whole idea of coordinating and collaborating is an effort right now that's a big emphasis. If the recommendation is going to be there for something to be done, that's the direction it would go. I don't want to delete something, but I'm just saying that 10 and 11, to me, go together to form something a little bit stronger and more realistic.

DR. COLLINS: So how about for that first bullet that instead you word it something like "NIH should encourage high-quality research on the ethical, legal and social implications of pharmacogenomics in collaboration with other HHS agencies."

DR. FITZGERALD: Okay. Great. That's good. I'm good with that.

Jim?

DR. EVANS: So moving on, I hope, the third paragraph or sentence, the last sentence seems so -- I'm not sure that the HHS would know what to do with that. That seems unbelievably broad, and I'm not in favor of leaving things in that aren't -- I think maybe you can explain. I missed the last conference call.

DR. FITZGERALD: Right. I think the idea here was just to say whatever is discovered in the research should then be followed up on. I mean, you're right, in one sense one could assume that would be done. I think the idea was rather than assume, state. But if you have a different way, a better way of --

DR. EVANS: I'm just struggling with it because it seems so broad, and I'm just not sure if I were in the HHS office I'd know what to do with it.

DR. LEONARD: The solution may not be something that HHS can do anything about either.

DR. PAREKH: I think that's a very important point. If one of these tests actually does limit access or decrease health care quality, it's not that HHS is going to have the magic bullet to solve that.

DR. EVANS: I think that all of our recommendations have the implication that they aren't just going to lie there. You could probably add that to every recommendation we make, so why do it here?

DR. FITZGERALD: Okay.

DR. EVANS: The one other thing that I'd ask is in the ELSI recommendations, it seems to me from previous discussions of the group that the possibility of litigation looms very large as a driver for the adoption of pharmacogenomics into medicine. I'm just wondering if that should somewhere be explicit in the ELSI chunk. There's a unique or a very powerful relationship between the legal issues and the --

DR. FITZGERALD: Right. So increasing medical liability is --

DR. EVANS: Maybe just acknowledging that that is likely to be or is seen by many to be a real driver of its adoption.

DR. WINN-DEEN: Jim, I think there's a section in the report that goes into that. We just didn't have it in a recommendation because we weren't sure that that was anything HHS really had control over.

DR. EVANS: That's fine.

DR. FITZGERALD: Debra?

DR. LEONARD: As we move through the recommendations, there are a lot where we're asking NIH to support research on various things. I would recommend that the subcommittee pull all those together and see how much we're recommending NIH to spend more money that doesn't exist and how to prioritize those, because that will probably be something that HHS will do, and we're not giving any relative priority to these things. So I think that might be useful.

DR. FITZGERALD: As you go back through the ones we did flag, again the ones with the little stars were the ones we were saying were of higher priority.

DR. LEONARD: Maybe pulling out all the ones for funding and looking at them as a group, because when you just kind of go through, money would be nice and money would be nice, and more studies would be nice, but what are our priorities to the Secretary?

DR. FITZGERALD: So pull this out? Do you have a format?

DR. LEONARD: I don't mean pull it out. I mean pull it out to look at it and see what you're recommending as an overall thing and see if you want to prioritize those in any way. I don't know if that then is incorporated into the recommendations, whether there's a little paragraph that says of all the funding recommendations our order of priority would be this. I don't know how you want to do it, but there are a lot of recommendations in there for funding with no prioritization for the Secretary.

DR. WINN-DEEN: The appendix at the back where it talks about what all the agencies are doing already I think is a reflection of let's call it current funding. So it's not like we're going from zero to something. We're just saying these are the areas where we feel funding should continue to be

applied to. I'm not sure that we're making any recommendation to increase overall funding for this but just to make sure that these, whatever five or six or seven areas, are addressed.

DR. LEONARD: But has there been an assessment of whether or not there are gaps in the current things being done relative to our recommendations where there are real gaps that need to be filled, as opposed to continued emphasis on things that are ongoing?

DR. WINN-DEEN: I think that's a great segue into item number 11.

DR. FITZGERALD: We can do that. Let's just address that, then, I guess.

Draft Recommendation 11. "An interagency work group should be established to review SACGHS' recommendations, assess whether and how to implement them, monitor the Department's progress, and report back to SACGHS. At the request of the agencies, the work group could also serve as a forum for discussion of specific activities." This is at least our attempt to get at some of the coordination issues that have come up and was a recommendation of our task force that seems to be okay.

Then looking at 11B, "HHS should assess the level and adequacy of resources being devoted to support the integration of pharmacogenomics into clinical and public health practice to be sure current and future gaps and opportunities can be addressed." So I agree, Debra, in one sense that there is a bit of prioritizing that we can do, but I think there's also some that we can say we are going to highlight these issues, and obviously the Secretary knows better than we about the resources and can do some of that prioritizing.

Yes, Linda?

DR. BRADLEY: Well, this is certainly something I would support, but whether you need to be a little bit more specific there. In other words, what comes to mind when I read this are areas where maybe we do need some additional funding; for instance, postmarket surveillance of tests that are entering practice, outcomes research that's already been mentioned. This might be a place to really put that, and also to resolve the identified gaps in knowledge that are going to come out of these different processes of looking at the evidence. So this might be a place to maybe specify some of those things.

DR. FITZGERALD: One of the things we wrestled with, of course, is how specific should we get. What do you tell the Secretary to do? What do you let the Secretary decide to do? But I think in a situation like this it's completely legitimate to put in a list of for instance or such as. If you would like to write that list, I'd be happy to give those as examples. Again, we don't want to necessarily dictate to the Secretary to do this rather than that, but certainly to give ideas, which I think is our mandate.

DR. HANS: On 11A, the task force may just want to consider whether adding a little bit of language there saying the Department should consider inviting participation of other federal agencies as appropriate, or something like that. There may be areas where other departments may contribute to that.

DR. FITZGERALD: Yes, and actually we did bat that around a little bit in the meeting. If you think that's a good thing, good. We were sort of on the fence about whether that was good or not.

We do have time. Wow. All right. This is good. Now, Yvette has worked on some of the ones we sort of flagged to come back to because we were wrestling with how to do them. Do you have that list? Why don't we start with number 2? Let's see how fast we can go through this.

Which one? Which slide, though? Do you know?

PARTICIPANT: Recommendation 2A.

DR. FITZGERALD: Okay. "HHS should provide FDA with the necessary resources to develop guidance documents about best practices for the co-development of pharmacogenomics drugs and diagnostics. This guidance should promote collaboration between the drug and diagnostic industries."

Oh, 2D? Oh, that's right, we did it backwards. I'm sorry, my fault.

This is the one, the Humanitarian Device Exemption regulation. "So that incentives for the development of orphan drugs are extended to pharmacogenomic tests that are intended to be used in conjunction with the orphan drugs," and this is the one where the exemption could lead to unanticipated and undesirable consequences. So is there a way that we can rework this to get to the goal that we're trying to get to?

Elizabeth?

DR. MANSFIELD: I might suggest that you don't recommend amending a specific thing but looking at ways to encourage pharmacogenomic testing in general rather than saying take this rule and change it.

DR. FITZGERALD: So instead of trying to be specific, as we tried to be there, to back off and be a little more generic. "FDA should investigate"?

DR. WINN-DEEN: Can I make a suggestion?

DR. FITZGERALD: Sure, please, anybody.

DR. WINN-DEEN: What I was thinking is that what we really want to recommend here is that the same incentives apply to orphan drugs as with their companion diagnostic. There are quite different incentives. There are financial incentives and only one test in the marketplace incentives.

DR. FITZGERALD: Right, so that's what I'm saying. Is just saying incentives going to be enough, or do we need to be more specific than that?

DR. MANSFIELD: I think that might work.

DR. FITZGERALD: Okay. Is everybody else comfortable with that?

DR. WINN-DEEN: That allows people to look at the legalities of it.

DR. FITZGERALD: Right, and we don't trap ourselves in a place where we don't want to be, absolutely. Is everybody good? Good. Excellent.

Next, Slide 39, 2C. "HHS should advance the further development of abandoned drugs by facilitating access to information about such drugs. Incentives will be needed to encourage the voluntary submission of proprietary data by pharmaceutical companies." We got hung up here because some people see this as doing two separate things. One suggestion during the break was that after the term "proprietary data" we add in "of abandoned drugs by pharmaceutical companies," making both paragraphs specific to the subset of the whole thing being abandoned drugs and leaving the broader incentive issues.

Where's Debra? I think this was her thing.

DR. LEONARD: I still want to know who it's being submitted to.

DR. EVANS: To get around that, we could put sharing, "encourage the sharing of data."

DR. FITZGERALD: "Encourage the sharing of proprietary data." Now, you would want voluntary sharing, I'm presuming.

DR. EVANS: Yes.

DR. FITZGERALD: Debra, to whom?

DR. LEONARD: Well, if it's sharing, then it's not submitting to someone, and that's fine.

DR. FITZGERALD: Good. All right, excellent.

Next, Slide 43. This was the clinical validity and utility. "In certain circumstances, public and private health plans should facilitate the generation of knowledge by conditioning payment of pharmacogenomic technologies on a commitment by test developers to collect data on the clinical validity and clinical utility of pharmacogenomics technologies. CMS' draft coverage with evidence development initiative may serve as a model for this practice." We're going to add here "analytic," I believe.

DR. EVANS: I think one of the problems several of us had focused around the issue of who decides clinical utility and conditioning payment based on the studies of clinical utility. I think there's a certain conflict of interest there. Obviously, insurers want to see clinical utility, but I think also it's up to the people practicing medicine to figure out whether things demonstrate clinical utility, and I'm just concerned about making the payers almost like the ultimate arbiter of conditioning payment based on their assessment of clinical utility.

DR. FITZGERALD: Reed?

DR. TUCKSON: Could we hear from CMS? I'm curious to see this from CMS' point of view. You already, I would assume, do this. I mean, I'm not sure what this does other than, again, argue for having the knowledge, the research, the data that tells you whether or not these criteria are being met.

DR. ROLLINS: We currently do determine payment based on what we perceive as what's considered effective. Even though physicians as well as others may feel that a particular technology might be helpful, our premise is we take a look at the totality of all the data currently available and make a determination of whether or not it's considered reasonable and necessary for a specific condition. Based on that, and I'm sure some people would say we shouldn't do it this

way, we essentially dictate what gets paid for and what doesn't get paid for. So what's currently being requested currently falls under the realm of what we do.

DR. FITZGERALD: Gurvaneet?

DR. RANDHAWA: I wonder if it would be useful to remove ourselves from a discussion about the payer's specific perspective here, because I think what we're trying to get at in this recommendation is, one, a mechanism to identify where the gaps in knowledge are, which is what the EPCs and the EGAPP and the other entities are doing, and the second mechanism is how to fund knowledge or outcomes research. The payer is just one element. Maybe there could be private/public partnerships with the payers, but there could be federally funded programs, there could be privately funded programs creating the evidence. It could be payers, it could be developers, it could be other entities.

So I think we're looking at a broader issue of how do we assess whether there's enough evidence, and then when there is not, how do we clear the new evidence, what are the mechanisms for that. The payer's perspective is just one element to this discussion.

DR. HANS: Kevin, I do wonder whether the recommendation in 6B actually covers the direction that this discussion is going. That is, insuring that when coverage decisions are made, they're made on a transparent basis and the reasons for those coverage decisions are provided back to the various manufacturers. So it really gets at the same point in some ways, without putting the circumstances of conditioning payment on, following up on.

DR. FITZGERALD: Gurvaneet, does that capture the larger issue that you were discussing?

DR. RANDHAWA: Yes, I think it's helpful to capture the issue and also to give some specific direction. If you are thinking there should be some collaborative efforts between different entities, payers could be one perspective. There could be other things we could focus on. If you think of some programs, then we could just give some examples of what programs. For example, from our perspective, the way I could look at this is if you're talking about creating new evidence, then the mechanism would be either funding R01 grants or funding cooperative agreements such as the CERT program or the DEcIDE network. But the EPC would be a different program where we're just assessing the currently published evidence or the systematic reviews.

DR. FITZGERALD: Reed?

DR. TUCKSON: What I think we're doing here is I think that what we are saying is that given that public and private purchasers make coverage decisions or payment decisions based upon demonstration of data, like clinical utility, clinical validity and the others that we've talked about in other sections, we urge that mechanisms occur that will have government working with various entities to facilitate that knowledge being developed, that information being developed so that these functions can be achieved. So without trying to rewrite it, when you go back and the subcommittee looks forward to it, which I'd remind you all that what we're trying to do with this discussion is decide whether you're going to let this report go forward for public comment, which I won't fast-forward to, but I would say that I think what you're going to find is that you've got several recommendations now that all speak to the same idea of facilitating the collection of knowledge, data, studies and so forth, by a variety of entities, and I think this just becomes one of those.

So I think the way you phrase it is in recognition of the fact that people are going to need this data to make these decisions, let's work together to try to get it.

DR. FITZGERALD: Okay, that sounds good. Do you want to write that one up?

DR. ROLLINS: I'd like to reiterate a point. It is true that CMS does have the coverage with evidence development for those promising technologies. A promising technology is one where there may be insufficient evidence showing that it's been effective, and that may be due to the fact that there are only a limited number of studies out there, but the studies out there do look promising. Unfortunately, they're not sufficient for us to say it is reasonable and necessary. So as I say, we do have a number of projects that do fall under coverage with evidence development, but as I said they've got to be promising, but unfortunately they don't have enough justification to show that they're effective. Whether or not any of the pharmacogenetic tests would fall under this category is something that would have to be determined by CMS or some other payer if they chose to go through that route.

DR. FITZGERALD: Does that fall under your general conceptualization, Reed?

DR. TUCKSON: Yes, sir. I'm doing my assignment, sir.

DR. FITZGERALD: Very good. All right. I like to see that.

Next, let's let Reed work on that.

That's it? Well, this is great. What I'd like to do now, then, is turn our attention to where we want to go. Obviously, we've gotten wonderful input today on a lot of these, very helpful, very insightful, and also brief, which is wonderful. So now the question is what do we do to revise the report and the recommendations based upon the input we have received, and then how do we move forward? I'm not sure exactly of the range of options here, but one thing I will suggest is the possibility that we take the various recommendations we have received on the recommendations, work those in, we could email people those recommendations in their revised form. Then what we'll do is the old if we don't hear back from you to veto the process, then we'll go forward with the recommendations as they are phrased. If you come back to us with a veto, then we will try to engage that process and eventually speed these things along so we can then move forward with the Lewin Group doing the stakeholder and expert interviews pretty much on schedule.

How does that sound to people? Cynthia?

MS. BERRY: I have just some minor editorial things that don't merit full group discussion and taking up time. Is there a process --

DR. FITZGERALD: You mean in the report?

MS. BERRY: Yes. Should we just tear this out and hand them to Suzanne or whoever, so we don't waste people's time?

DR. FITZGERALD: Sure. If there's information that you think would be good to be in the report, let us know, please. We've already indicated with some things -- we could rework the report, too. Absolutely.

Does that process sound reasonable to everyone? If so, I think that's what we will do. We will work as quickly as we can. I'm going to be very unpopular with some people here, but okay. We will try to get those back to you. We'll tell you how much time we need to have your responses, and then if we can pretty much move ahead, we will do that so the Lewin Group can get going on the stakeholder interviews and we can seek public comment. If that is okay with everyone, that is what we will try to do, and I believe that that pretty much wraps up what we were told to do today.

DR. TUCKSON: Isn't he good?

(Applause.)

DR. TUCKSON: Masterful, masterful.

It's time for lunch.

I need support. I assume and hope that the boxed lunch deal got circulated in time for the boxed lunches to be made. I hope that Chira did not stop the process when it got to her.

The other thing is what time do we come back? The people who are not in the boxed lunch group know that there's this terrific restaurant right next door. There's the cafeteria behind you and something forward. You can turn left or turn right and food will be there waiting.

We come back at exactly at 1:45. So we'll see you at 1:45.

(Whereupon, at 12:50 p.m., the meeting was recessed for lunch, to reconvene at 1:45 p.m.)