Pharmacogenomics Session Full Committee Discussion
Facilitator: Emily Winn-Deen, Ph.D.

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

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

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

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

(Slide.)

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

(Laughter.)

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

And then the other important thing is if anyone on the committee—particularly since we have three new individuals joining us this time who maybe have some new thoughts to share and new perspectives, if there's anyone who has some additional things that they believe we should be addressing, we're going to open that up for discussion as well.

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

DR. RANDHAWA: Thank you, Emily.

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

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

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

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

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

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

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

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

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

Now before I venture further, let me make it clear that I'm discussing things that are not within AHRQ's purview. We do not make coverage decisions nor do we have any regulatory powers to make any decisions to approve medical products.

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

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

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

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

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

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

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

So thank you for considering my comments.

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

(Slide.)

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

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

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

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

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

DR. TUCKSON: So the bottom line is what document should we have in our hands, Suzanne, so we know where we're tracking?

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

DR. TUCKSON: Called?

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

DR. TUCKSON: All right. Great.

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

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

MS. GOODWIN: Right.

DR. TUCKSON: Right.

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

DR. TUCKSON: Right.

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

DR. TUCKSON: Thank you.

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

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

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

(Simultaneous discussion.)

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

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

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

DR. WINN-DEEN: The new recommendations.

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

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

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

(Laughter.)

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

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

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

(Slide.)

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

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

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

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

Debra?

DR. LEONARD: Can someone comment about how feasible it is to do this type of co-development? Since it seems like it may work logically for the target pharmacogenomics where

you know the drug is useful for a particular target like herceptin, HER2neu or Gleevec, BCRabl, and then you would know what test you want to be doing. But if it's for adverse events or dosing or those kinds of things, how feasible is this to even think that you're going to get two of these coming out at the same time given how clinical trials work?

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

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

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

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

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

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

(Laughter.)

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

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

end of the day but at the moment those are the statutory and regulatory requirements and require some type of reg change to change that.

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

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

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

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

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

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

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

DR. WOODCOCK: All diagnostics, yes.

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

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

DR. WINN-DEEN: Kevin?

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

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

DR. WINN-DEEN: Francis?

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

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

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

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

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

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

DR. WINN-DEEN: Okay.

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

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

DR. TUCKSON: I'll pass.

DR. WINN-DEEN: Okay. Debra?

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

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

DR. LEONARD: Yes.

(Laughter.)

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

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

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

DR. TUCKSON: Right.

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

DR. TUCKSON: Right.

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

DR. TUCKSON: Okay.

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

DR. TUCKSON: Right.

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

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

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

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

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

DR. TUCKSON: Okay.

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

DR. WINN-DEEN: Okay.

DR. WOODCOCK: Speaking for myself.

DR. WINN-DEEN: Okay. Agnes?

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

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

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

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

MS. MASNY: Okay.

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

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

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

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

Steven?

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

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

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

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

DR. WINN-DEEN: --have look up tables—

DR. TEUTSCH: --and that comes later but I do think you need to say it takes more than just telling people. It takes systems change to make it happen and I do think we need a recommendation of that sort.

DR. WINN-DEEN: Okay. Andrea?

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

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

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

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

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

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

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

DR. LEONARD: Why not?

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

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

DR. WOODCOCK: Right.

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

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

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

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

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

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

DR. WOODCOCK: Eventually it will. As we develop more targeted therapies, the treatment effects of those therapies will be larger. The benefit will be larger and that's true with some of the therapies we have now. They are directed that way. Therefore, when you have to compare

new therapies against that—let's take the best example, which is the—which is HIV drugs. All right. Those are actually personalized against the virus so that whatever virus you have, whatever its mutations, you get a drug that is targeted to that.

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

DR. WINN-DEEN: Francis and then Jim?

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

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

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

DR. COLLINS: That could be a bit circular.

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

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

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

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

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

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

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

DR. WOODCOCK: Well, we have inherited the technologies that have been available to us over time and what we're talking about now is a change as we have new technologies that we can use but we don't quite know how to use them yet. So we're doing the best we can under the circumstances, I think, is the best answer we have. We have really advanced the treatment of cancer and many, many people are cured of cancer treated who weren't before but we can do better in the future and that's—we just need to figure out the pathway.

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

Steve?

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

basis for saying, okay, this is what we think you should do and have some standards for clinical guidance that can then be translated into practice in a variety of ways.

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

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

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

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

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

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

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

DR. TUCKSON: Thank you.

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

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

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

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

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

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

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

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

DR. WINN-DEEN: Kevin?

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

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

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

(Slide.)

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

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

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

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

DR. WINN-DEEN: Okay.

DR. GUTMAN: Because I'm not sure that the agency has actually made a clear public statement about that so I don't have any objection at all to having that left on and having that perhaps made more clear.

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

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

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

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

DR. LEONARD: Before I have a heart attack—

(Laughter.)

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

DR. TUCKSON: What's a better term?

DR. LEONARD: Laboratory developed diagnostic tests.

DR. WINN-DEEN: Laboratory developed test.

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

DR. TUCKSON: That's important.

DR. LEONARD: --it really—they should be called laboratory developed tests because they are developed under CLIA regulations and in New York State, at least, we have to go through a

whole New York State approval and review process, which is very much similar to probably what the FDA would implement.

DR. TUCKSON: Right.

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

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

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

DR. TUCKSON: That is important.

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

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

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

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

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

I know Francis is very anxious to say something.

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

Francis?

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

So the very existence of your prior committee, the SACGT, and potentially, therefore, of SACGHS tracks to this very issue. SACGT, once they came into existence, did an extensive amount of consideration of this and at that point the legal opinion was that FDA had statutory authority to oversee in-house testing. That has subsequently been questioned whether that was

the right interpretation but it was the interpretation back in the late 1990s and SACGT did, in fact, spend a lot of their time on this issue and made some specific recommendations about getting FDA involved.

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

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

Debra?

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

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

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

(Laughter.)

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

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

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

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

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

Suzanne?

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

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

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

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

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

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

MS. CARR: In the CLIA?

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

DR. FERREIRA-GONZALEZ: Yes.

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

DR. FERREIRA-GONZALEZ: Yes.

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

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

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

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

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

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

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

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

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

DR. WINN-DEEN: Right.

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

DR. WINN-DEEN: Right.

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

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

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

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

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

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

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

DR. LEONARD: Yes.

DR. WINN-DEEN: Yes.

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

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

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

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

DR. WINN-DEEN: Whether HHS.

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

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

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

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

Next?

(Laughter.)

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

(Slide.)

So the issue that has been identified, and I know that a lot of people are aware of this, is that there's two different human subject protection regulations. One is the HHS Common Rule, which governs most of the clinical studies done through NIH funded grant kind of mechanisms. And then there is the FDA Title 21 which governs clinical trials done in preparation for an FDA submission.

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

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

(Slide.)

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

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

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

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

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

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

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

Regarding the issue of lack of harmony or inconsistency or conflict, it's important to analyze where is the inconsistency coming from and there could be three possible levels. One is at the

level of the words used in the regulations, the actual text. I would assert that there is little substantive difference between the two sets of regulations we're talking about to say that that is the source of the problem, although if someone wants to challenge that assertion it would be helpful for someone to specify where is the regulatory language differing that's causing the issues and the concerns.

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

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

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

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

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

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

DR. WINN-DEEN: Steve?

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

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

using everything from quality controlling your instrument systems to doing some method study to doing some basic research.

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

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

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

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

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

DR. GUTMAN: That would be very wise to—

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

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

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

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

we're going to have to wait until we come back after lunch. So just for those who had their hands up.

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

DR. WINN-DEEN: Debra?

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

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

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

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

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

FULL COMMITTEE DISCUSSION (CON'T)

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

Emily?

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

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

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

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

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

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

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

DR. WINN-DEEN: Yes.

DR. LEONARD: Okay.

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

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

(Simultaneous discussion.)

We're having a consultation here.

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

DR. : Yes.

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

DR. : Yes.

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

DR. : There's wording also.

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

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

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

DR. TUCKSON: All right. Regardless—

DR. WINN-DEEN: So we lost two?

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

(Simultaneous discussion.)

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

DR. : Yes.

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

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

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

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

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

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

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

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

Sylvia and then Andrea?

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

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

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

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

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

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

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

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

DR. CAROME: Well, from our perspective--I suppose you're talking about samples that have been anonymized to where all identifiers have been permanently removed or the samples have been coded in a way in which the researcher receiving the coded specimens—there are prohibitions against them never receiving the key to the code. We've essentially declared in a guidance document a year-and-a-half ago that that's not covered by our regulations because it doesn't involve human subjects. So we stepped back and removed ourselves from that and so it's the issue of to what degree do the FDA regulations apply and they've tried to do some carving out. I think to the extent that this is limited to FDA moving that forward as far as I can under current statute that's where this should probably best go.

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

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

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

DR. WINN-DEEN: Okay. Sarah?

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

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

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

All right. So let's move on.

(Slide.)

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

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

DR. WINN-DEEN: Right. I agree.

DR. EVANS: Yes.

DR. WINN-DEEN: Okay. All right.

(Slide.)

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

(Slide.)

So the staff put together a potential—this was an area we had not made a recommendation on as a task force and so this is a new potential recommendation on potentially asking HHS to promote public access to the data on pharmaceutical products that have failed to demonstrate effectiveness in studies involving a general population cohort but might be candidates for a more tailored approach.

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

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

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

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

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

Steven?

DR. TEUTSCH: I am not directly connected to a lot of the senior level for a pharma company but, as I think most of you realize, there's now a clintrials database, which has been the subject of a lot of discussion but the trials are now at least posted on clintrials.gov so that the nature of those trials are made available and it seems to me that the process would be for those that are interested in looking at those that have failed compared to the—you can probably get the results of some of those trials because there's a commitment to get some of that information out that the ones that have "failed" or even the ones that are successful that it would be up to diagnostic and other companies that have ideas as to how they could be optimized to get back in touch with the

sponsors and develop the kind of collaborative relationships that we talked about earlier with the public-private or private-private kind of discussions about the additional studies that might be conducted. So I'd probably tie it to something that already exists rather than developing an entirely separate process.

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

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

Francis and then Agnes?

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

I would take just one point, though, to say that NIH does conduct Phase I, II and III trials, especially for rare diseases. It's not purely a pharmaceutical industry activity. But in those circumstances, again it's a little hard for me to see why you would need some sort of special inspiration for sunshine to be directed on that process because anybody conducting a clinical trial is going to be highly motivated to try to figure out whether the drug did something good for somebody. And in the current era if the specimens are there and if there's a reasonable idea about what genetic variance might have correlated with response, I think the people running the trial are going to jump all over that so this one does seem a little anomalous.

DR. WINN-DEEN: Agnes?

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

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

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

(Slide.)

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

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

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

So any comments, requests? Francis?

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

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

DR. COLLINS: Which is it?

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

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

DR. WINN-DEEN: Right.

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

DR. WINN-DEEN: Okay.

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

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

DR. COLLINS: But before you throw it away, the way you were verbalizing this a minute ago, though, I think is a circumstance where you're in the post-marketing phase. I mean we talked about warfarin this morning where a drug has been around a long time. It isn't necessarily ideal in terms of the incidence of side effects and you've got a chance to try to do better by trying to use pharmacogenomics to improve dose adjustments. It does seem to me there is a research priority for drugs that have been around a while that we haven't fully capitalized on and I would have thought that this committee would want to endorse the importance of that kind of activity which probably won't be supported in the pharmaceutical industry because if you have a drug that's already approved you're not going to be terribly motivated to try to narrow its scope or add an additional complication to the labeling that might scare away some prescribers. So this may very well turn out to be our job for NIH and other federal funders.

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

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

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

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

DR. COLLINS: Right.

DR. : That's number five.

DR. WINN-DEEN: Yes. I thought we already had that as a recommendation.

DR. EVANS: I mean that's a pretty central feature--

DR. WINN-DEEN: Yes.

DR. EVANS: --to everything we're saying. I think the confusion arises because of this issue of new innovations.

DR. COLLINS: Okay. Back in the earlier one.

DR. EVANS: I don't think that is really what anybody was—

DR. FERREIRA-GONZALEZ: How about G? You're talking about post market surveillance.

DR. WINN-DEEN: Yes.

DR. COLLINS: That's really adverse drug reactions as opposed to dose adjustment although they're connected.

DR. LEONARD: 5A is recommending these—to encourage rigorous prospective randomized studies to test whether promising pharmacogenetics findings actually translate into improved patient care, which is what warfarin is all about.

DR. COLLINS: Right.

DR. EVANS: We could add something on there about for new drugs and for established drugs, right?

DR. WINN-DEEN: Yes.

DR. EVANS: I mean to make that clear.

DR. WINN-DEEN: Okay. All right. So in the interest of moving forward here, we'll just pass that opportunity by to make a recommendation. I think that was fairly clear input from the team.

(Slide.)

This was an area of intended use population. I think this gets back to what we were just talking about that we would like to see all of the trials using a genetically diverse set of patients doing the trials and should it be apparent that there is some potential subset to try and work towards understanding what the actual genetic basis for response is versus saying that one racial subset appears to respond better than others.

So I think this was trying to get at the issue of--the way Bayh-Dole ended up getting approved is that we really—we still don't really understand the genetics of what's going on there and we're using race basically as a surrogate marker for whatever the actual underlying genetic marker is. So that's just a recap of recommendation three.

(Slide.)

For the next issue, which was Phase IV clinical trials for PGX, the question arises that in a normal Phase III trial for use of a companion diagnostic you probably still have a relatively small subset of people being tested and if you're trying to use your pharmacogenetic test to avoid, say, adverse reactions you really want to follow that out into a Phase IV to verify that that actually is working as hoped.

So the question arose, and maybe FDA can clarify this a little bit, as to what FDA can actually do. There's a requirement sometimes for Phase IV studies but there's also—it has been widely reported that Phase IV studies don't seem to happen as agreed to and I don't personally understand the mechanism for either requiring Phase IV studies or what obligation that pharma companies have to conduct them, what enforcement FDA has if they don't conduct them. Is there just some education that we could get on that subject?

DR. GUTMAN: Allen, you're going to have to field this because I actually don't know what the authorities for Phase IV studies are.

DR. RUDMAN: I'm not quite sure what the questions are actually.

DR. WINN-DEEN: Well, so my specific question is if you could explain to the committee how a Phase IV study comes to be requested by FDA and what mechanisms there are available at FDA to assure that one that's requested actually gets designed and executed.

DR. RUDMAN: A very interesting question and it's a very appropriate timing. Phase IV commitments—when you have enough information to approve a drug but you have certain questions that you really want to follow up on to optimize the dose or for other reasons like safety or whatever reason there is. These are sometimes very limited, sometimes not at all and sometimes quite extensive.

I'm not going to get into the question of when or why a company should be doing this or the timing on it. I think that's a whole different issue for the moment.

In terms of—what I would say is the companies do sign off to do this at the time. It's part of the agreement for the approval and so they are committed to doing it.

I'm not quite sure if particularly for the older applications if the timing was really ever specified. I think that's part of the issues involved.

DR. WINN-DEEN: Okay. So is that changing now that when they—if a

company was to be approved tomorrow and part of that approval was that they agreed to do a Phase IV study, is there agree to do it with—to have it designed and begun within a certain period of time and completed and reported by a certain period of time?

DR. RUDMAN: My understanding is that the FDA is now looking into improving the process and really looking into doing it in a systematic manner rather than doing it ad hoc case-by-case. So they are trying to really improve the entire process.

DR. WINN-DEEN: Okay. I guess what I'm trying to get to is are there some tools that FDA would like to see in their tool belt to help them get that done that we could make a recommendation on in terms of assuring that Phase IV studies, once agreed to, are actually executed or is that something that you think FDA has under control?

DR. RUDMAN: Well, they are actually starting it now and I think that's what's going to come out very shortly. For me to say right now I think would be to preempt the process the FDA is trying to go through right now to really improve it systematically.

In terms of the issues you have up there, identifying genetically based subpopulations as a condition for enrollment, that's true. Actually this goes to the question of trial design, whether you're going to be looking at enrichment designs or adoptive designs--

DR. WINN-DEEN: Yes. So let me flip—

DR. RUDMAN: --or other designs.

DR. WINN-DEEN: --to the recommendations.

(Slide.)

So maybe this is—should all new drugs that require a companion diagnostic be subjected to Phase IV study? I think that's a question. I'm not sure that we should take that out of the hands of the experts at FDA who are actually looking at the data but that was a potential recommendation.

The other question is in terms of keeping track of adverse events. Is the database and the reporting structure sufficient to allow that to really be properly tracked in the absence of a Phase IV study but just out in general use?

DR. RUDMAN: In terms of option one, I don't know if you really want to mandate Phase IV clinical trials. In cases where—you know, safety and efficacy has been shown to be in all commerce. Do you really want to require them to do another study when you've already shown that a product works in all commerce? I mean the way it's going to say "mandated" seems to implying that you are using the word "required." Okay. So I'm not sure if that's really what you meant.

In certain cases certainly it might be beneficial but I think that has to be worked out.

In terms of option two, I'm probably not the right person. Probably Dr. Seligman, who has just received—he's in a new position currently but he's in charge of safety, Office of Drug Safety. And my understanding from his talks was that actually we have both passive and what you might call active methods for looking at adverse reactions, including databases from a number of

different organizations, where they look at the—they go out there and actually search their data as against waiting for the data to come in.

So, I mean, that's my knowledge of it but I think Dr. Seligman would be the best person to talk about those in detail.

DR. WINN-DEEN: Okay. Any comments from the task force? I mean, I personally agree that I don't think mandate is the right word in option number one. Maybe they should consider that for each drug at least with a companion diagnostic whether there's actually enough dataset to not want to do a Phase IV but I'm not sure it's up to us to mandate things to FDA.

Steve, I'll let you respond to that and then Francis had a comment.

DR. GUTMAN: Yes. I mean, you are emphasizing here the drug side which seems to me to be appropriate. Of course, the device side also has the capacity. It's not called the Phase IV study but it's a condition of approval study. So we actually have some tools for follow up on our side. The good news is that there's—perhaps because of the Vioxx fallout—there's renewed interest within devices at doing a better job at post market studies and surveillance so I think we're taking this much more seriously.

The bad news is we don't have a rich culture certainly in the diagnostic area to draw from so we're sort of chartering new ground here but the news that sort of trumps it, and actually HER2 is the case in point, is that you can't stop people from studying and observing the behavior of the—at least on the diagnostics. The pathologists are very intrepid beasts and they are still arguing—actually still arguing about IHC versus FISH versus proficiency tests. So I actually think the pathologists will worry about this for you on the diagnostics side.

(Laughter.)

Our—we do have efforts to look at—again on the diagnostic side—look at the passive reporting system. They are about to try and convert it to an electronic medical device reporting system. The good news is that will make it easier to use, friendlier, easier to sort through the data. The bad news is garbage in/garbage out and that that won't guarantee we're getting high quality data so that's still something to work to attain.

We're also fooling around with a new system, part of MEDSON, called LAVNET in which we are also trying to on a very pilot basis explore active surveillance as opposed to passive surveillance. Certainly this is an exotic, sexy enough product area that if we could identify the right partners these would be the kinds of products we'd be interested in following. We're not really interested in hemoglobin or glucose or sodium in quite the way we used to be. Not to suggest that they aren't important.

DR. WINN-DEEN: Right.

Francis, you had a comment?

DR. COLLINS: Yes, but this is more about option two.

I think the goal of option two and of AERS, in general, is to try to identify those rare instances where an already approved drug is causing side effects but not at a high enough frequency that it was necessarily picked up in the Phase III trials. This is an area that I think is of great interest to

the public and to the FDA and we've had quite a lot of discussions between FDA and NIH over the last year about ways that this might be facilitated, both in terms of a reporting system but from a perspective of trying to not only figure out what happened but why it happened. How could you not only have a reporting system but something that is linked into obtaining a biospecimen on the individual who has suffered an adverse reaction so you could begin to try to assess what the reasons for that might be. Now we have such mechanisms as doing whole genome association studies and it becomes possible to actually do that even with modest—hundreds or so—numbers of cases you might have sufficient power to do that.

So I guess the AERS system as pointed out here does not necessarily have the search-ability that you'd like to have in some ways because of the lack of a controlled vocabulary but it also doesn't provide you in many instances with a link that gets you actually back to the individual and gets you a biospecimen, and that seems to me maybe that ought to also be highlighted here. If you're going to have a really effective system it ought to have all of those pieces so it becomes a real engine for research discovery and then for implementation of what you've learned as far as better public health.

DR. WINN-DEEN: Sure. Okay. That's a good comment.

Steven?

DR. TEUTSCH: Just a couple of points. One is I didn't see anything in here that is particular to pharmacogenomics that we've made the case as to why this is any different than any other kind of drug issue in which case we need to have general things. I think Dr. Collins made a good point that the AERS system is pretty good for rare events that are unusual that are easy to find but it's terrible for finding common things like myocardial infarctions that are not likely to even be reported within this kind of a system and that's the reason for developing the entire other set of safety related studies, whether it's surveillance studies that are more systematic, registries or other kinds of things to find those kinds of things, which I suspect are at least as great interest as these rare events but that's true for any kind of drug discovery process.

I think we'd have to make a case as to why we think things—what are the things that are different for pharmacogenomics that would warrant this or else we just indicate that this should be done in a general sense.

DR. WINN-DEEN: Well, I think the question probably comes back to what Francis said about getting this biospecimen. Ultimately if we could understand—if we could identify those who had these events, it might potentially be possible to get a specimen from them and do the research so that you could find whatever the biomarker is, whether it's a genetic marker or protein marker, expression marker, whatever, so that a companion diagnostic to weed those people out could potentially be developed. I think that's sort of the link to pharmacogenetics in this—

DR. EVANS: We ought to say that. That's what we ought to say.

DR. WINN-DEEN: Yes. I mean, in my mind that's really what it's for. It's not just to find adverse events. So what? The whole point is to get—

DR. EVANS: Apply pharma—we should encourage ways of applying pharmacogenomics to figuring out these adverse reactions.

DR. WINN-DEEN: Okay.

DR. TUCKSON: I think, Steve—I see that we have another committee member's hand, I just want to make sure—I think, Steve, what you both, and James, are trying to get at here is that the preamble to all of this in terms of about how we get to why there is a recommendation, why is it—what is it about pharmacogenomics that makes this particular topic especially important or especially relevant? I think we do need to be real clear that we—that we are not solving—that we're solving a problem that has somehow or another been identified as being important. I think that that's really what you're getting at and I think what we're sort of doing is we've got the cart behind the horse right now because we're jumping into the recommendations.

So the question to make sure of is either that your question is making sure that we are, in fact, responding to why this or your question is have we made—have we convinced you that there's a problem that has to be solved?

DR. TEUTSCH: Right. I mean, I think the point I heard here was that you should use pharmacogenomics as part of solving problems that are detected with any kind of adverse event system. I mean that you can make a recommendation about. That's a unique application of pharmacogenomics to understand safety issues as opposed to anything unique about pharmacogenomics that makes them have specific safety issues because there are plenty of small studies out there that are just like these that will be for limited populations where it would be applicable.

DR. WINN-DEEN: Right. So, unfortunately, we've got sort of processing where we have sort of the contextual report being presented to you separately from the recommendations. Our hope is that when the thing comes together that what you'll have is you'll have in the report here's the problem, here's the issue, and then here are some recommendations that address that issue.

So we'll make sure that this part here about adverse events really is listed in that section where—I think everybody would agree that there's drugs that have been pulled off the market because of adverse events that were probably quite beneficial to a large number of people but aren't available to anyone now because a small number of people had bad stuff. So there's—I think there is some incentive on both sides to try and figure it out to report the events, to get specimens and get the research done to really figure out what's going on.

DR. TUCKSON: I'm not sure, though, that—by the way, I appreciate that. I was trying to listen to it carefully. Did we decide, though, is it because—is this issue on the table because of the concern about bad things or the opportunity that this provides from a technical point of view to have benefits across all of health care? I think that's really what Steve is getting at and I'm not sure which of his two questions is what we're—is the problem we're solving. Is this a problem we're solving or an opportunity that is available for this field to contribute across the board, and I'm not sure which one this is.

DR. WINN-DEEN: Well, I mean, personally I think if you're going to talk about adverse events, the horse is out of the barn. The drug is released and presumably it has been released without some kind of a test. Otherwise you wouldn't have released it. So you need to have Phase IV studies to find—or Phase IV or some kind of registries or monitoring to find adverse events and then you need to have a system to see if there's a rescue strategy possible to identify those people who are at highest risk from taking a specific drug.

Did you want to say something? I'm sorry.

DR. RUDMAN: I'd just like to point out there are actually two sides of this. One is certainly the adverse events side of it to minimize adverse events but the other side is the efficacy side. It is actually that both equally—not equally important but they both have a significant contribution. There was the brief discussion this morning about Iressa and the possibility of using Iressa where you have increased efficacy in subpopulations.

The other side of it is, of course, the safety issue. This really addresses the safety part of it but you might want to think about addressing the efficacy side of it.

DR. WINN-DEEN: Right.

Gurvaneet?

DR. RANDHAWA: That was actually my point, also. I think one of the issues is the drug may be approved on the efficacy side on surrogate markers and not on health outcomes which may actually be different once it goes in the real world. I'm not sure that it's only FDA's concern. I mean the other health agencies, whether CMS or AHRQ, are equally interested in finding out what the health outcomes are of drugs. So I would suggest broadening the recommendation to look at not only the safety but also the benefit side and making it beyond just FDA but other relevant HHS agencies who may be interested.

DR. WINN-DEEN: Okay. I think we're going to have to do some more work on that one and put it in the right context.

DR. TUCKSON: One of the things you might want to consider as we go forward is—just as we look at the available time—is how much energy to put on the options and how much energy to put on the actual topic area.

DR. WINN-DEEN: Right.

DR. TUCKSON: So you might, as you guide us through that, making sure that we do have consensus on the G's and the H's and the so forth.

DR. WINN-DEEN: Right. So we're moving along here.

DR. TUCKSON: Thanks.

DR. WINN-DEEN: Okay. So we're going to sort of switch gears here on to some of the issues that were raised on direct to consumer marketing of pharmacogenetic tests.

(Slide.)

In some ways pharmacogenetics is a simpler case than an inherited genetic disease but the question is still whether a consumer is equipped to receive pharmacogenetic data and act on it in the absence of a health care provider partner. So that's really just framing the issue.

So there's four potential recommendations here. I'll just go over them briefly and then we can discuss the subject.

(Slide.)

I think it really boils down to at what point is the consumer informed enough to work with the information.

So the first option is that FDA should require the labels of the pharmacogenetic tests that are offered directly to consumers to include information sufficient to enable them to make their own informed decision on the use of the product and actually interpret their results.

The second option is that FDA should require as a condition for pre-market approval that companies offering PGX tests directly to consumers without the involvement of a health professional should make available telephone mediated genetic counseling.

(Slide.)

The third option is that you could move things to a level that's a CLIA waived test that's approved for sale over the counter and at the point where something is approved for sale over the counter then you're definitely marketing directly to consumers even if what's available over the counter is just say the sample collection device that's then sent into some central laboratory for processing.

And that anything that isn't approved basically for over the counter use would have to involve consultation with a health professional.

And the fourth option is, just due to the complexity of this whole area, the Secretary could encourage congress to pass legislation prohibiting the marketing of PGX tests directly to consumers without the involvement of a health care provider.

I just want to say that this is sort of the spectrum. It was not intended that we pick all of these but that we use that as sort of a discussion range for what we really want to say on where we think direct to consumer marketing of pharmacogenetic testing is today. There certainly are people that say you should know your CYP2D6 genotype and talk to your health care provider about it any time you have a drug prescribed to you. That's sort of one school of thought.

And the other is that this is really something that the physician should be managing and not the consumers.

So I just want to maybe have ten minutes of discussion on this and then try and come to some conclusion of where in this range of options we'd like to say something if we decide we want to say something at all about it.

DR. TUCKSON: By the way, as you contemplate this and make your decisions on this, do remember that we have got our direct to consumer activities outside of this and so one of the things you want to make sure you keep well in mind is the synergy between things that we're doing, and so as you make perhaps policy here that will be one thing where you have another process of informing this decision through our discussion around the FDA and other oversight on DTC so just keep that in mind.

DR. WINN-DEEN: Okay. Kevin?

DR. FITZGERALD: Yes. I just wanted to—looking at the first two, as we mentioned before, if there are difficulties with labeling and having the physicians gather the appropriate information

from the labels, I'm not sure we should dump that on the consumer directly. So option one doesn't seem to be terribly viable in that regard.

Then the second one—I guess we probably run into the difficulty that we had before when we were talking about genetic counseling and the idea that if the company was going to make available this telephone mediated genetic counseling, what criteria would there be to say that these people are adequate to the task of doing the genetic counseling? Can you do single disease genetic counseling? Do they have to be masters level? Can there be nurse—we went all through this before.

DR. WINN-DEEN: Right.

DR. FITZGERALD: So rather than get into that swamp again, I'm tending more towards the other side of your options there.

DR. WINN-DEEN: Okay. Yes?

DR. EVANS: I'm just trying to think about who would be using this and in what context and whether it's worth thinking about. I don't think people are going to be using this for decisions about the dosing of their Sudafed when they have a cold. Right? So you've already got—you have physicians integrated into the process already in the sense that for most of the things we're talking about a prescription is required. Right? So who is—it's going to have to go through a physician, don't you think? Is that fair?

DR. WINN-DEEN: I personally hope so but that's just my personal opinion.

DR. EVANS: No, I'm just—well, practical standpoints—

DR. WINN-DEEN: Right. No, you're right.

DR. EVANS: --aren't the physicians going to implicate into this?

DR. WINN-DEEN: Joseph?

DR. TELFAIR: I had a comment on that but you already made it.

DR. LEONARD: Well, one of the concerns I have is not only does the physician write the prescription but then your health insurance only will provide coverage for the amount that the physician has written you for so you can only take the dose that your physician gives. You can't go self-dosing. But on the other hand I've heard reports of people who have had adverse reactions because of a physician not taking into account the pharmacogenetic variability of that patient and they go get their CYP2D6 or whatever done and take it to their physician and their dose gets adjusted and they feel much better. It's a New York Times article that I use sometimes when I'm talking about pharmacogenetics.

So I'm not sure since physicians are not integrating pharmacogenetics into clinical practice that we want to take away the right of patients to at least have access to this if they need it.

DR. EVANS: Right, and patients—

DR. LEONARD: Or could benefit from it.

DR. EVANS: And patients bring things to us all the time and say, "What about this? What about that?" And that's part of practicing medicine.

DR. LEONARD: But maybe what we do want to do is—I mean as Reed was pointing out, maybe we want to encourage the FDA and FTC to take a specific critical look at the marketing and use and safety of pharmacogenetic tests in this FDA-FTC collaboration that we initiated or encouraged them to do. Maybe that would be the right framework in which to put this and then the FDA and FTC have expertise in doing this and could look at the pharmacogenomics that's being marketed direct to consumers.

DR. WINN-DEEN: So let me ask you how you guys feel about option number three. So if a test—this is a completely hypothetical but if a test was to pass the requirements to be marketed over the counter to a consumer with all the requirements for sixth grade language readability and a clinical trial that shows that people can understand the directions and properly interpret the results that come back, is that a scenario that we would feel comfortable? Is there any scenario we would feel comfortable--I guess, is really the question—in direct to consumer marketing? Not just any genetic testing. Not here I do want to specifically limit it to pharmacogenetics which we had identified, SACGT, as sort of the lowest risk genetic testing environment. Is there any scenario in which we would feel that that might be okay?

DR. LEONARD: Jim is right because nobody is going to be able to do anything with it because the physician is the only one who can write the prescription.

MS. AU: I think for the most part genetics is so complicated that most public—they don't really understand it. To allow them to choose how their genetics could affect their drug or how the drug will affect by the kind of gene that they have. A lot of them, they just don't understand it.

DR. EVANS: I don't understand how my car works either.

DR. WINN-DEEN: Right.

DR. EVANS: And I don't have to get permission to buy one. I mean—

(Laughter.)

I don't know. I think that since there already is a mechanism in place—people aren't writing their own prescriptions and aren't saying I think I'll start taking warfarin and dose it with GX, I think that—three isn't too bad it seems to me because there are circumstances. People should be able to—if somebody really wants to find out whether they are a CYP2D9 metabolizer or fast metabolizer or not, it's okay. I don't think that's threatening or toxic information to them so I don't think we should be too proscriptive.

DR. WINN-DEEN: Barbara?

MS. CHEN: A lot of time people get information that will over alarm them
that might not be that great anyway.

DR. WINN-DEEN: Well, of course, it would depend on if you got something through in an over the counter scenario that all of that stuff would have had to have been addressed as part of going through—there's quite a rigorous approval process to get anything approved for over the counter use and there's a relatively small number of tests but I can tell you that people who are taking

home pregnancy tests might be alarmed by the results. They might be happy and they might not be happy.

(Laughter.)

But we don't tell them they can't take the test.

(Laughter.)

DR. EVANS: It just seems to me that unless we can identify and see a real risk to people—I mean that's—we obviously need to step in and make recommendations if there are risks to people but I'm having trouble figuring out where there would be a big risk to people and then getting their genotype.

DR. WINN-DEEN: Okay.

DR. EVANS: But I'm open.

DR. WINN-DEEN: I'm going to let Barbara say something because she has been very quiet today and then we've got Andrea and Gurvaneet.

DR. McGRATH: I think I'm just mimicking what we're saying. I think that we can decide in this room that it's good or not good to have direct to consumer advertising but it's out there. It's not going to end. It's going to just increase, I think. So you can't make a recommendation to say there should be no direct to consumer advertising because it's out there and people take prescription drugs, whether or not they're prescribed for them, so those are the realities. So I think it makes more sense to sort of make some—maybe some of the ideas that Debra Leonard suggested and make some recommendations about drugs in general and educational materials but I think it would be kind of silly for this committee to say there should be none where I think there's no question that it's going to happen.

DR. WINN-DEEN: Okay.

DR. TUCKSON: Thank you. I want to suggest given that we've got time on the agenda for DTC tomorrow and it's on the agenda formally, maybe we might just—I think you've given us a good sense of it. Let's revisit this when we get there. I'm real worried about the fact that we've got 45 minutes left and we've got to get through a bunch of other ones.

DR. WINN-DEEN: We're actually doing okay here.

DR. TUCKSON: I'm glad you're confident.

(Laughter.)

I'm the one that gets blamed if we don't bring the train in on time. She's gambling with my money here.

(Laughter.)

DR. WINN-DEEN: Okay.

DR. TUCKSON: By the way, if we do finish before the allotted time, we'll come back and talk some more about DTC.

DR. WINN-DEEN: Okay. Well, I'm going to skip over it.

(Slide.)

This is prioritization of pharmacogenetics research needs. Obviously in any society there's a finite funding pool so the question is how do you prioritize what areas would be most useful to go after? One potential straw man recommendation was that HHS should convene a group of experts to develop criteria for prioritizing pharmacogenetics research needs according to feasibility, public health need and impact on public health. The group should also assess both current and potential PGX projects and rank them according to their relative priority.

So my first impression on this, again taking the chair's prerogative to make a comment, is that this sounds a lot like an NIH study section or the process that NIH would go through to identify before it put out a request for proposals the areas that would be most beneficial. So I'm not sure we need to convene a new group of experts.

I don't know, maybe, Francis, you can comment on how NIH comes to decisions on funding.

I don't know if Rochelle is still here.

DR. COLLINS: Yes. I was also looking around the room because it would be really helpful to hear about our pharmacogenetics and genomics efforts that are underway at NIH, which are organized particularly through NIGMS with Rochelle as the major leader. So this involves many institutes. There's a pharmacogenomics research network that you may know about that has been in existence for several years. There's a database.

DR. WINN-DEEN: Is there coordination with the other AHRQ and all of those groups that might be interested in outcomes research?

DR. COLLINS: Yes, although I can't tell you the details and I'm sorry Rochelle is not here to answer that question.

DR. WINN-DEEN: Okay. So I think as a recommendation that it's good to have a group of people who are well informed to create a prioritization list. I don't have any problems with the basic concept of this recommendation. I just didn't want it to appear that we were making a recommendation when there's already activities ongoing within HHS. So maybe we need to just do our homework a little better on exactly what's going on.

DR. COLLINS: Yes, given that at least in this meeting we haven't heard a report on what's already underway in this regard from someone like Rochelle, it seems a little premature to endorse a recommendation of this sort which implies more is needed.

DR. TUCKSON: And maybe as we follow up on this from her, let's also try to be clear about to what purpose this prioritization—I'm not sure I know what it is we—again, what do you do once you—is it—prioritization for what purpose is not—

DR. WINN-DEEN: Well, I think that the concept was to examine sort of from the public health benefit point of view, if government money is to be spent on something, how does that decision making process come into being. Should you do esoteric disease X or should you do warfarin?

DR. TUCKSON: No, but the key thing was that—

DR. WINN-DEEN: So I mean there's some—

DR. TUCKSON: --I think the operative issue was, again given the relevance of this committee, if government money were to be used—

DR. WINN-DEEN: Right. Specifically HHS money.

DR. TUCKSON: --then what would be the priorities. Is that basically what this—okay.

DR. WINN-DEEN: But I guess my question is do we need to make a recommendation that we should—HHS should convene a group of experts or is such a group of experts already convened? If we think it's already convened then this is sort of redundant. If we think that there are some issues and it needs to be more broad based specifically across agencies then maybe this is a worthwhile recommendation.

DR. COLLINS: So I think there—

DR. TUCKSON: Isn't it—

(Laughter.)

DR. WINN-DEEN: Well, it depends upon if we approve going with the large population study or not.

DR. COLLINS: I think it's fair to say there is good coordination between FDA and CDC and NIH. What I'm less sure about is some of the other HHS agencies but again I guess because setting up groups of this sort involves a fair amount of energy and time commitment on the part of the people who have to set it up and who have to participate in it, it would be nice to be sure that this is not something that this group would already agree is covered and I think it may be.

DR. TUCKSON: So we will get the input.

DR. COLLINS: Yes.

DR. WINN-DEEN: Okay.

DR. TUCKSON: Good.

DR. WINN-DEEN: Okay. See, Reed, we're just moving right along here.

(Slide.)

So this recommendation really was trying to look at the more complex side of drug metabolism and looking at more than just a one gene at a time, either systems biology or looking at

multigenic issues. We know that there's a lot of what—dietary influences on metabolism. There's drug-drug interactions that can affect drug metabolism.

(Slide.)

So the question was whether we wanted to sort of move to promoting a wider thinking process in the research into understanding drug metabolism with a goal being that if you understand it in a more holistic way you can have even better predictor tests available and so I think warfarin is a good example.

We've heard there's two genes but they contribute not everything to how you get to an effective dose and there still are other biological factors that have to be taken into account. How do we make those pieces come together so that you can have the most effective treatment for patients?

So I don't know where we are with trying to think more broadly in terms of the grants that are being funded and starting to really understand that it's not a one gene kind of a thing in a lot of cases where we're going to have to deal with more complex—not just more complex genetics but also understanding all the other sides of things. There's this big environmental study that's going on as well. I don't know how much influence that might have.

So I think this was really intended to just outline pretty clearly that it's a complicated area and as we move forward the answers may be also more complicated and the need for—it may not be a test but a panel of tests or whatever that give you what you really need.

Francis?

DR. COLLINS: A couple of comments. I mean one is that this is not just about drug metabolism. This is also about variations in the target for drugs and all of the other things that are involved in the pathway.

DR. WINN-DEEN: Right.

DR. COLLINS: So maybe that ought to be broadened a little bit. Again this is really, what you're describing here, very much a central goal of this collaborative enterprise, a very significant one for NIH. The Pharmacogenomics Research Network, the PGRN, which is associated with this database, Pharm-GKB, that attempts to try to collect a lot of this information about pathways and how variations in particular genes and proteins may play a role in differential drug responsiveness. So I don't think it would be fair to imply that somehow this is not already considered a very high priority. It's hard stuff. I mean anything that gets into the realm of systems biology is hard stuff and that's sort of what you're talking about here is marrying pharmacogenetics with systems biology.

DR. WINN-DEEN: Right. So I guess we could come down on just saying that, that it's hard stuff and that this is going to take some devoted time and effort to really study properly with the recommendation being to make that time and effort to do so or we can just throw up our hands and say way too complicated, let's save that for somewhere down the road and tackle the things that are more straight forward today. So again just trying to get some sense from the committee of the spectrum of opinions on where we are and what things we can practically recommend at this point.

DR. RANDHAWA: I will be happy to give one part of the spectrum of opinion here. Both in this recommendation and the previous one there is sort of an assumption here that understanding more about genes is going to play a larger role in improving health outcomes of a given disease. Warfarin is a great example. I've been hearing a lot about it in this meeting and it's an appropriate example. But one can say, okay, we can understand all we can about genetics and understand precisely what dosage to give starting out therapy but how does that factor into some therapy that's going to be given for five years, ten years? How many weeks the patient may decide not to take the drug, how about dietary factors that may influence the role of the dosage of warfarin or other medications that may influence bleeding level that has nothing to do with genetics?

So in terms of research funding, should we be thinking about ways we can improve compliance and adherence to the warfarin where if you make an impact of 20 to 30 percent of patients who are compliant to maybe 30 percent of patients being compliant, they will have a maximum benefit of both as opposed to understanding what about genetics at the front end of dosing. So I think it's a good discussion to have.

In terms of prioritization, we perhaps need to think about different approaches to improve disease outcomes and not just to focus on genetics and how genes may improve the outcomes.

DR. WINN-DEEN: Okay. Other comments?

Can we get in touch with Rochelle if she's the right person to just give us a little synopsis on where we stand in terms of the more complex approach here? I mean if you think staff can just get in touch with her and do that or whatever is the right chain of command.

DR. COLLINS: If we could track her down and try to get her back here before 4:00 o'clock, would that be useful?

DR. WINN-DEEN: Potentially.

DR. COLLINS: We'll try.

DR. WINN-DEEN: Okay. Francis, maybe if you can even just get her on the phone. She doesn't have to physically get back here. Okay.

(Slide.)

So the next area that—we're just going to keep going on here because we're going to try and make as much progress as we have or we can--really concerns the issue of neglected diseases or orphan diseases. So I guess sort of two separate things. One is neglected diseases that affect large numbers of people but they don't happen to reside in the countries that have a lot of money to address them so they don't get a lot of attention because the health care dollars in those countries are spent on more fundamental things like food and water supply and maybe, if you're lucky, vaccination.

So the question is, is there a role that we should be thinking about or is pharmacogenetics just so far off the spectrum there that in limited health care dollars it's never really going to be applied?

And the other end of the spectrum is for rare diseases that are in developed countries but they're just so infrequent that they don't have—again this is a commercial incentive issue. There's not

enough people with the disease to develop the research that really is needed to ascertain if a pharmacogenetic approach might be helpful. There's a gap between the number of individuals who qualify for orphan drug status versus orphan diagnostic status. So we just—I wanted to just sort of frame those two issues and then we can go through where we are with that.

Comments, Kevin?

DR. FITZGERALD: Yes. I was just wondering—I'm not sure that it's all encompassed by saying a system for fostering for neglected disease because I was just wondering—I mean you can have the same disease and still have neglected populations of people—

DR. WINN-DEEN: Sure.

DR. FITZGERALD: --who share that disease. I thought since our emphasis here is of public dollars for public health, maybe we should add that in there somewhere to say or neglected diseases or it's not so much like saying, geez, I'm neglecting this disease. It's the populations that are being neglected. It's the people that are being neglected. I don't really want to foster the disease but I think that would put the focus back more on the public health question because here in Washington, D.C., we can talk about the neglected populations that share perhaps the same disease that other people do and the question is can this technology give us another way of addressing that situation rather than saying this is going to solve this disease and say is this going to help us address this particular public health issue.

DR. WINN-DEEN: Okay. Joseph?

DR. TELFAIR: Okay. Two things. One is—and they're both sort of in this—sort of spills out of the same recommendation. This issue is addressed pretty well by some organizations already. For example, the American Public Health Association has some clear policies along the lines of what Kevin was mentioning in terms of the issue of drugs for populations themselves that are neglected or under served, and there's a lot already that exists there and it's very easy to get.

The other thing along the same lines is that Dr. Alexander, as you know, with rare diseases and I think that it may be worthwhile to get an informed opinion about that part of it—of what's—because there's a lot of discussion already and there's a lot of discussion that has been had, and there's actually, from my understanding from presentations by him because of the committee that I serve on, is that there is some work already in that direction. I'm not quite sure. I don't know if Dr. Collins knows or not and whether they've had interactions with Dr. Alexander in rare diseases or not but I know that there has been some discussion. I think it would be really helpful to this group—this committee before something is decided to find out what's really going on there, and I think it would be very informative to do. So I'm just recommending for this particular set of options to actually have a conversation with those two groups and the staff can do that because the policies by APHA are pretty straight forward and I'm sure when Ms. Terry talks to you tomorrow she can fill you in as well about what's going on there with genetic alliance and also there is contacts and I can give you names a little bit later for APHA. But also with Dr. Alexander, I think, having him, himself, or someone from his office talk—either come and talk or have a conversation about can give you some informed decision. If there's a committee that's going to have a meeting on this already then maybe the committee itself can meet them because they're just right here. I know that he come to every one of the other meetings that I go to and I've heard this conversation so I'm just bringing that up.

DR. WINN-DEEN: Okay. Thank you.

Debra, did you have something?

DR. LEONARD: This recommendation seems kind of like mom and apple pie. I feel a little uncomfortable making a recommendation about how NIH should pay attention to populations of diseases that maybe neglected either the population or the disease. When you really want to get kind of the best bang for your buck, if you will, and if cardiovascular disease is a leading killer of Americans or spent cost of health care dollars, then I don't know that we necessarily want to be recommending that they not spend money there and spend money on rarer diseases. So I'm not quite sure—while I agree that it would be nice to take care of absolutely everybody and every disease, also my concern is with neglected diseases. Is there the basic research of appropriate therapies, et cetera, being done so that pharmacogenomics would even have an impact at this point or where are we in the treatment of those diseases?

So I just feel quite uncomfortable with this recommendation.

DR. WINN-DEEN: Did you want to say something?

DR. TELFAIR: I just want to say I think both of those questions could be addressed by the organizations that you have. I mean, I guess the way I see this is part of the work of the group is to advocate also for those that we can but I think it should be a very—advocacy needs to be in a real sense realistic. So there are these policies where they are realistic and they take into account a lot of these other issues, and I think it will be—before the group even decides to run or not run with this—to really listen to what those other things are saying and I am addressing this to try to—I'm adding on to what you have said but I do think that would be real helpful.

DR. WINN-DEEN: Right. So maybe, Suzanne, we could get in contact with these folks and maybe have them join the task force meeting for a short period in September just to sort of take a little bit of that task force time to understand what's going on already.

DR. TUCKSON: Just as we do that, again I want to—I think just we want to keep in mind again the committee—the need for—as we get to the end of this process here, a sense of prioritization, a sense of what are the things that we can do as a committee and what things you can't do. And I think that one of the things I appreciate in Emily's comment—the same thing we did on the coverage and reimbursement report—and for those that are new to the committee, I would urge you to take a good look at the front piece of that report. We sort of basically put our work in the context of a health care delivery system that is already stressed and extraordinary with 45 million uninsured people, da, da, da. So at the end of the day there is, as Emily, I think, appropriately has introduced into this conversation, a sense of reality. I think we also had a moment ago a discussion about the NIH committee that may or may not be working—the HHS committee that may or may not be working in terms of coordination. That gives you a sense, also, of prioritization.

So as you think about all these recommendations, which we are going through appropriately now—we're doing the hard slogging through the mud of each of these recommendations, at the end of the day we have to really keep in mind we've got to come back and sort organize these, prioritize these, which are the ones that make sense. Of course, you can't get to that elegant conclusion until you punch each of these out and see what's there and turn the rock over and see what it means and that kind of thing. So I just want to just keep that context in mind.

We're not going to do everything. You can't do everything. You've got to focus in on what makes sense so we have to keep drilling through this process.

DR. WINN-DEEN: So we have a half an hour in our discussion time.

(Slide.)

We have a number of things to cover. Measurement of health outcomes was an area where we already had a draft recommendation and we discussed it at the previous meeting.

Gurvaneet, did you have anything else you wanted to say on the health outcomes because I know you're quite interested in the outcomes area?

DR. RANDHAWA: Yes. I would again like to stress that not all the different kinds of study types and methodologies that we can use to gather real world data are in here so there is—so I'm looking at recommendation 5A and there's an emphasis on regular prospective randomized studies to test whether promising PGX findings actually translate into improved patient care.

It's not clear that that is really the best study design to get into translational research. And here when I say translational research, I mean post-marketing translation into clinical practice. And whether it's through pragmatic clinical trials or whether it's through information gained in registries or some sort of additional database or health plan database, it's not quite clear here as to what the advantages and limitations of these different data gathering activities are and how we can use all of them to get a better prospective of not only the benefits but also the harms and the patient safety.

DR. WINN-DEEN: Okay. So I think that's an area where we can maybe ask the Lewin Group as they make the next revision of the report to look at these sort of categories of outcomes research and how they might be done and at least set the stage in a little bit more functional detail.

Barbara, did you have something?

MS. McGRATH: I just want to jump in real quickly. I'm been chewing on this all morning. Dr. Woodcock said something really intriguing to me when she was talking about the early—early on trying to talk about the field of pharmacogenomics and how important it potentially will be and barriers to its discovery. She said something--unless I misunderstood her saying that randomized controlled trials will not be the only paradigm, that we need a paradigm shift. I thought that was a revolutionary statement. That's why I wasn't sure I heard it correctly.

DR. WINN-DEEN: Particularly for FDA.

MS. McGRATH: Well, yes. So I wondered if that really is true and we say that are we—is the bureaucracy ready to accept that. Would NIH and the FDA really accept evidence-based coming from something other than RCT and you bringing that up with outcome research reminded me of that again, though she was talking about it on the front end as well. So I guess I would just—I don't know if that's one of the recommendations that we think about because there's other recommendations in here about research process but I—it was an intriguing statement.

DR. TUCKSON: Just only a friendly amendment to your question is maybe not so much what NIH accepted. I think the operative group is would CMS accept it and would the private payer—purchasers of health care accept it. I think that's really where the issues are and it's a legitimate question and one that I think is worthy of further exploration.

DR. TEUTSCH: These are going to be really central issues for things particularly as we deal with rare events and small populations so it's unique to many of the things that we're dealing with and AHRQ has certainly taken the lead on many of these to try to develop better methodologies that will pass the rigor test that people will find acceptable.

I think one of the things that we could do is to talk about an effort to really solidify the method so that we do have some good alternatives to RCTs that are credible which have dealt with the major issues that are the threats to validity problem because most of these are observational and that can put all of this on a much firmer footing when we are not going to have RCTs or we're going to have to retrospectively go back through trials and deal with them. We need that kind of methodology. I think that's something we could ask to be developed.

DR. WINN-DEEN: Okay. Other comments?

DR. TUCKSON: I just want to make sure we don't lose something here. I think that what's important again as we come back to the prioritization and the definition of—I mean what is it that our committee can do? I think, Steven and Barbara, that you're both sort of focusing in on this continuing challenge of genetic exceptionalism. What is it about the pharmacogenomics that's different than other things? What are either the opportunities or the challenges that it presents? Why are those issues important to the American people? Why are they important for this committee to decide that it's worthy of attention?

I think that I just want to keep all of our very smart committee members thinking about that question. How would you write that paragraph? I'm not asking you to do this at this moment but I think you have to really start to write that paragraph. How is—what is it that is so special about pharmacogenomics that it requires or provides the opportunity for different things that, therefore, require an investment in time and energy, whether it's Francis' point about calling for a committee takes time from busy people, that we would feel strongly enough about it to ask for that, or money because we think it ought to be specific new studies that need to be funded or new regulations that congress ought to pass.

I mean I think we have to be very—we're getting to the point where we have to be very disciplined about why it is that this is special and what is the opportunity that we have to make a difference in ways that are meaningful that need to be addressed that would not otherwise be addressed were we not to exist.

You should think about writing that paragraph. I think that will discipline your analysis of this a little bit.

DR. WINN-DEEN: Okay.

(Slide.)

I want to try and move ahead here. We have linkage and compatibility of clinical databases. I think this is an area where there is a lot of effort going on between the group that's focusing on this whole electronic medical records issue and trying to rationalize FDA databases and the clinical database that is part of your FDA submission.

I don't want to really dwell on this but if people have some specific comments, particularly the new folks, in terms of anything else that we should be concerned about to make databases that are in existence more useful and searchable so that basically if the knowledge is already there you

can get to it. So that's really not about new knowledge as much as it is about really trying to pull together the knowledge that is existing somewhere in space today.

Sherrie?

DR. HANS: Actually I think my comment is more relevant to the previous recommendations. I didn't realize we were going to move off 5C. HHS should identify federally managed databases such as, et cetera, et cetera. I would just encourage the committee to think about other federal databases or federal opportunities. For instance, the Department of Veterans Affairs have electronic medical records on almost seven million veterans that might with collaboration between VA and HHS might provide considerable opportunities for health outcomes research.

DR. WINN-DEEN: Do you think it might be useful to just—as much as we sort of pull together all of the activities within HHS in terms of different things they are doing, to try and pull together in one place a list of databases and what they—sort of the basics of what they have or what their point of being is?

DR. HANS: You mean all of these different federal—

DR. WINN-DEEN: Yes. Just so you sit here and you say NHANES, HCUP, what do those really have in them and what exists today, and then we can at least have a sense of where there already is data. To task someone with trying to make databases compatible is, I know, quite a monumental thing to think about but would there be ways in which a controlled vocabulary, for example, within all HHS databases or all—

DR. HANS: Yes, I was actually thinking of something very different in encouraging collaboration to address the purpose of where you're going rather than looking at compatibility.

DR. WINN-DEEN: Okay. All right.

Joseph?

DR. TELFAIR: I just want to contribute. I agree with the recommendation but I just want to say that it already exists, what you just asked. MCHB, HHS, HRSA, MCHB has a blue book on outcome data and it already exists and it looks at pretty much all the databases in the HHS system, and some that are related, and then linkages and contacts and that sort of thing. It's a volume that already exists and I can give the reference to the staff.

DR. WINN-DEEN: Okay.

DR. TELFAIR: If they need it.

DR. WINN-DEEN: That would be really helpful, I think.

DR. TELFAIR: Sure.

DR. WINN-DEEN: I mean if it already exists we don't need to be worrying about it.

DR. TELFAIR: The part that doesn't exist is what Ms. Harris was recommending that kind of needs to be worked out but the other part of deciding what are the actual mechanics, it's done.

DR. WINN-DEEN: Okay. Can we not have side conversations, please?

I'm learning.

Okay.

(Slide.)

So then we had a recommendation on evidence base for economic value of pharmacogenetics. I think we all recognize that this is a really important part of showing that something will benefit the system and either reduce the cost of adverse events, reduce the cost of being on the wrong meds, reduce the cost of hospital stays while you're getting on to the right dose. If you're going to put a test in front of a drug, which has a cost to it, hopefully you're saving that cost in spades down on the other end. If not, you're just going to be increasing the barriers to access and the cost of delivering medicine.

(Slide.)

Again I think this is one that we've had in the book for a while and if there's other comments from any of the new folks, I'll just ask you to send those in to the staff.

(Slide.)

Government officials' knowledge of pharmacogenetics, this was one of the gaps that was identified as a place that maybe we should say something about that. I think it really is aimed at the people that are having to interact with decision making in terms of pharmacogenetic tests so either people who are involved in regulating a test getting on to the market, reviewing filings or the people who are regulating the payment for that test and how it would be integrated into clinical practice. They ought to have some basic understanding of what this is and so whether there's a way that all those kind of people that are involved throughout HHS and making decisions about pharmacogenetics can get a little primer on it so they have at least some basic set of knowledge that they're working from to make informed decisions rather than uninformed decisions. So that was really, I think, the source of this recommendation.

Reed obviously has a comment.

DR. TUCKSON: I would urge that this not be one that we would put a lot into. I think it's sort of pejorative and I mean this sort of basically says that the people that are doing—reviewing science and so forth and so on don't have mechanisms to keep up and they're not—without our prodding, they would be slipshod or uninformed or not doing continuing education. If that's the case they ought to be out of here.

(Laughter.)

DR. WINN-DEEN: Okay. Well, we'll just put that as the recommendation. Learn what you need to know or you're out of here.

(Laughter.)

Any other comments?

I think we've acknowledged that education about new fields is an important thing and so I think I'll differ from you a little bit in that we ought to encourage and make it possible for the people who need this knowledge to get the knowledge they need through some kind of continuing education mechanism. I think that was really the point of this to provide continuing education for those that need it.

Any other comments?

DR. FITZGERALD: We could probably solve that by just getting rid of insufficient understanding and just emphasize the education piece. As law makers have an insufficient understanding there. Just change it to law makers have a continual need of being updated on these issues or something like that would probably solve the pejorative aspect.

DR. WINN-DEEN: Okay.

Debra?

DR. LEONARD: Why are emphasizing "law makers" as opposed to everybody else who is going to learn about pharmacogenomics, too?

DR. WINN-DEEN: Well, I don't think we emphasize law makers without taking into account everybody else but—

DR. COLLINS: The recommendation sounds as if you're focusing this on HHS staff and I think I have to agree with Reed. The way it's currently phrased it's not just about the insufficient understanding in the preamble. The recommendation itself implies that HHS staff are generally unable to get themselves up to speed on any new topic unless somebody comes along and beats it into them and I'm not sure that would be well received by HHS staff.

DR. WINN-DEEN: Okay. That's definitely—okay.

DR. : Government workers.

(Laughter.)

DR. WINN-DEEN: You never know. My budget cut my continuing education this year.

DR. TUCKSON: Go to school.

(Laughter.)

DR. WINN-DEEN: Anyway—okay. I think I'm going to skip to liability issues because this is one that again we sort of danced around a little bit at the previous discussion.

(Slide.)

Whenever you have some recommendation that says you should do something this way, if you don't do something this way you chance—take the chance to be sued about it. So really the question was aimed at if there's a recommendation that a test should be used in conjunction with prescribing a drug, if you don't use that test, if the patient—there's several things. If the

physician doesn't order it, is there a liability? If the patient refuses it and then has an adverse event because it was prescribed anyway, is there a liability?

So really we—not that any of us claim to be experts but we just thought that we should probably highlight that there—like any other medical procedure—there is some liability potential here and the question of when does something become "standard of care". Does it become standard of care when FDA approves a test and a drug? Does it become standard of care when more than half of the insurance companies pay for it or when there's a physician consensus statement that it should be used in a certain way? So we just wanted to highlight the potential for pharmacogenetic testing to create some liability issues and particularly I think the physician failing to order and the patient refusing to be tested are the two key areas that would be of concern.

Debra?

DR. LEONARD: What is also the liability of having genetic variability on a drug label but no dosing recommendations? So I mean there—we're struggling with this at New York Presbyterian hospital because we're trying to figure out how to use pharmacogenetics when there's genetic variability in the label. One of the things we're considering is what's our liability for not testing for this genetic variability and yet there's not enough information out there to effectively us it clinically. So there's also this gray area of liability.

DR. WINN-DEEN: Right. So that goes back to when is something standard of care really. When you first discover it and you sort of know about it a little bit or when you've gotten to a clear—well, it's on the drug label but there's not a dosing recommendation. So then is it—so the question is should we try and—as part of this process—create a recommendation for either a group of experts to really establish what would potentially be used as legal precedent then or should we just discuss this in general terms and not really say much beyond that other than a study is required and the price of medicine is a difficult thing to regulate.

DR. LICINIO: I would like to say that I agree that the issue of dosage recommendation is crucial because it boils down to that in the end. I mean the test is useful to some degree but it basically has no practical utility unless you change the dose. If you're going to take the drug at the same dose there is—I mean you can be reassured by the test if you are a known metabolizer. But the point is really to address the dose and then the question is how do you address it and that's what's sorely needed.

So just saying that the dose needs should be addressed based on the results is not going to go anywhere. What is the doctor going to do, if anything? That's the crucial issue for the field right now.

DR. EVANS: I'm not sure what we're really doing with this recommendation in the sense that I don't think that the Secretary or our committee is going to be responsible for setting the standard of care. The standard of care is kind of a multifaceted thing and that applies whether we're talking about pharmacogenomics or whether we're talking about the best way to do a particular procedure.

So I am—I mean, I think this is a fine sentiment. I am not sure, however, that it's real productive to have—I mean, who would this committee—so this committee is supposed to explore these issues and devise strategies and recommendations but who would those go to and what power would they have. I just—I have trouble with—

DR. WINN-DEEN: Yes, so I guess—

DR. EVANS: --I mean I think we need to really focus on advice to the Secretary that is practical tangible advice that you should act on this and you should do this. But as far as kind of what Debra referred to as apple pie and mom stuff, I don't know. I mean I think we run the risk of diluting our recommendations by having too many things here that sound good but I'm just not sure they are practical.

DR. WINN-DEEN: Right. Well, like I said, these were just up—they were areas that we identified at the last meeting that we really hadn't addressed so wanted to try and address them to have some conversation. There is nothing wrong with saying that this is a hole we don't want to step in or that it's inappropriate for this team to really comment on.

DR. FERREIRA-GONZALEZ: It might be more appropriate maybe to have the recommendation to HHS to develop infrastructure to have greater communication when the clinical practice guidelines or dosing recommendations are given that they could give to the right professional organizations or members of the different societies.

DR. WINN-DEEN: Right. Well, I think that's in some of the other recommendations.

DR. FERREIRA-GONZALEZ: Yes. So that will go back to that one.

DR. TUCKSON: One of the other things that you might consider here is again which of these recommendations are things that will support the involvement of the medical societies in actually being able to write the guidelines and the standards of care. So that may mean something to do with again having the available evidence and answers to the kind of questions that they need to have answered and so forth. That may be the way to tie some of these things together.

DR. WINN-DEEN: Right. I guess I was just concerned a little bit of say FDA approval was the bar then that's definitely an HHS thing and one would have to think about that as part of doing an FDA approval that once that happens that that has certain repercussions and we really haven't dealt with the whole ethical dilemma and payment dilemma of what if there's a test that's a companion diagnostic that's required but the patient refuses the test. Are they still eligible for the drug or not? And if they are still eligible then does that create a sort of shower of stuff that happens where everybody says I don't want to pay for that test so just skip the test and give me the drug.

DR. TUCKSON: We have got three minutes to do two more so you guys are going to have to really move quick.

DR. WINN-DEEN: Okay. So I just want to go over what the other two are and then again solicit your written—well, there's actually three in my little book here, four, five.

DR. TUCKSON: I will tell you what then—

DR. WINN-DEEN: Okay. So let me just say that these recommendations 9 through 13 in my slide set here are ones that we talked about before. It would be useful to have input from anyone who hasn't had a chance to give input on to these areas. So it's basically best practices, distribution of information, interpretation of results, Medicare coverage. It would be quite interesting to know what the process is for Medicare and CMS could make a decision on that.

And ultimately we would like to just probably make a recommendation that when we have electronic medical records they have a mechanism for including genetic test information.

I think those are pretty straight forward.

What I did want to take the next five minutes on is if there's also anything that people have for comments back to the Lewin Group on the draft report that they have written, if there is other issues—

DR. TUCKSON: Let me try it this way because I think this is important. Let me just ask you a question back. What we have done, and the committee should be commended, and Emily, for not only organizing but leading us through a very wide ranging menu of possibilities for this topic. I think that what the committee has certainly benefited from, from this discussion, is that we are pretty well now sort of all sort of up to speed on the varieties of things and we've actually shared some consensus building around what we think are important and not important, and we've fleshed these out.

I think we all have the sense that there's more work to be done on these, more sense of prioritization, more grouping, more lumping, sort of more analysis of this, and that is very important but I don't think there's any way that we as a committee, as we learned from the coverage and reimbursement process, unless we just slog it out detail by detail and keep going over and over it, you just don't get to a shared understanding where you actually can vote on anything as complex as this a couple of meetings from now. So this is good.

Now, Emily, what you are saying is that we've got this draft report in yellow that has a lot of text to it. The question becomes how does the committee read this now given everything that you have sort of gone through—you've got a sense of learning more about what these things mean, what's important and not important, how do you go through this and then comment on it and to whom do you comment in the days to come, and then what happens with those comments and how does it go forward?

So the question, Suzanne, is how do your staff support—want to solicit the committee's input on the yellow pages?

MS. GOODWIN: First of all, just for clarification, the yellow document in here is a lit review and is not a draft report. That is what the Lewin Group is working on right now. They're taking the background and they're going to be reorganizing it and setting it up so whatever recommendations are in there, there is some background information. There is laying out of the issue or the gap that has been identified and helping to set up the recommendations so that's what they're working on right now.

What I think would be most useful—and Sandy can correct or add to it—what I think would be most useful is to get some input from the committee members and ex officios about are there any specific topics that are not currently in the lit review but that you think are important that should be added as background and somehow help set up some of the recommendations.

DR. TUCKSON: Okay. Well, then—all right. So that's one way to do this is again you're providing information on this literature review and what's in it and what's not in it.

The second mechanism here--and let me just sort of by way of doing this formally and with extraordinary appreciation thank Emily for her taking the lead on a complex task. I think you all

know and we're going to say it with sadness tomorrow but that Emily transitions off the committee at the end of this meeting and that is with sadness.

Let me just stop right now and thank you, Emily, very much for what you did.

(Applause.)

Now, what this means is that James Evans is no point. I'm deliberately not looking at him because I'm making sure that he's not withdrawing--

(Laughter.)

--given how much work there is and how complex this assignment is as you've seen and how hard it is. It's good. But James has got the point and passing the baton to James.

Now there are some other people on this subcommittee I do believe. Do we know who they are?

MS. CARR: Well, we neglected to include the names of the other task force members in Emily's slide presentation so our apologies for that but Jim, of course, who is going to become the chair, and Julio is on—Julio—and Debra and Kevin. And did I miss—

DR. WINN-DEEN: A lot of help from the ex officios.

MS. CARR: And the ex officios have been enormously helpful and we keep—and we must keep badgering them to help us identify not only the gaps but the common sense solutions that can make the recommendations of the committee tangible and actionable by the Secretary.

DR. TUCKSON: Great.

MS. CARR: CDC, NIH, AHRQ, DVA has been on as well—Veterans Affairs has been on the pharmacogenomics task force—no, they haven't. Maybe they want to be. Maybe they don't want to be.

(Laughter.)

DR. TUCKSON: How did Sherrie get out of that that easy?

MS. CARR: Yes. But any other ex officio agency—

DR. TUCKSON: That was smooth.

(Laughter.)

MS. CARR: --can. We are planning to have an in person meeting of the task force in probably the very beginning of September where we can really have a revised draft—rather a draft report of the committee together by then and also have—prioritize the recommendations.

DR. TUCKSON: Okay. So I guess the challenge I'm sort of asking—and I'm going to turn to Suzanne who is very good at staffing these things—she's top notch. So you've got the examples, Suzanne. You said that at some point people can comment to you on the gaps in the yellow page literature review and analysis.

If they also wanted to inform some ideas for James to think of outside and the committee outside of the literature review, should they also send that to you or directly into James?

MS. GOODWIN: I think they can send it to me.

DR. TUCKSON: Definitely Suzanne. All right.

(Laughter.)

DR. EVANS: And my—I would just have one plea that anybody who happens to read it, my general sense is that we have a huge smorgasbord of issues and not that we're missing ones. I think that where we've been really successful is identifying a whole slew of things and I would just reiterate what I mentioned a minute ago. I think that recommendations get diluted when there are too many of them. So I would be most interested in what people think about what goes beyond the purview of this task force, what really doesn't make sense to address in the isolated context of pharmacogenomics, and try to focus. That's one of the things I think we have before us.

DR. TUCKSON: Well, with that, I really again want to thank you, not only Emily but the committee. This is good hard work worthy of our effort and I think that we've brought everybody up to speed and so now we're ready to move to the next stage of this project.

Jim, I'm glad that you're able to take the baton.

With that, we are not bad actually. It's 4:05—really 6, but I'm going to give myself a leeway--4:06, and we will reconvene for another exceedingly important discussion on the large population study. We'll do it in exactly ten minutes, which makes it what—something like that—let's say 4:15. 4:15 right on the money.

(Whereupon, at 4:06 p.m., a break was taken.)