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

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

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

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

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

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

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

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

(Laughter.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. GUTMAN: This isn't exactly my shop, but I work very closely with the people who are making these labeling changes. They are my colleagues. Would it be your view that we should either be asking

for more data before we're making labeling changes, or would it be your view that we should be more conservative in making the labeling -- in other words, are we being too aggressive? Are we being premature in terms of what we're doing or asking the wrong questions?

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

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

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

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

DR. LEONARD: Yes.

DR. EVANS: So this actually gets to the comment I was going to make which isn't so much a question for you. In looking at the translational needs and the research -- and since I'm on the task force, I should have probably caught this before, but I don't think the most important possible issue on here is starkly enough highlighted. That is, we can recommend and we will see all kinds of pharmacogenomic tests coming out, but what is really desperately needed are prospective outcome studies. Right? Even the great stuff that's come out on VCOR and warfarin has not yet shown that it makes a difference in outcome.

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

DR. WINN-DEEN: Francis?

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

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

When it comes to something like the Amplichip for P450 variance, this is much messier, as you all were just saying. I mean, to mount such a prospective study in that instance, you'd have to mount 20 different

studies for 20 different categories of diseases and different drugs and where you had a much less precise opportunity to assess what looks like efficacy and what looks like a side effect. So that one is really, I think, going to be a very tough issue.

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

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

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

Probably the strongest literature -- we didn't look at all. There are 41,000 articles, so we didn't look at every article on the enzyme, but we did do analysis of various parts. We saw relative strength to the literature for psychiatric neurologic diseases, but it was only relative strength. There are actually publications that do make tentative dosing recommendations, and we were anxious to get the tool out for a variety of reasons.

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

(Laughter.)

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

(Laughter.)

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

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

DR. COLLINS: So that's part of the pharmacogenetics network that NIGMS has been leading the effort on for some time. I don't think that particular EELSI program contemplates actually conducting clinical studies. This is to do research of a more general sort on the ethical, legal, social, and economic consequences, but not to actually conduct such studies. That's going to have to be done by the respective

institutes that are interested in that particular topic, as Heart, Lung, and Blood now is with warfarin and which we hope will get underway on that basis. Given the tight budget constraints, these are complicated, expensive studies to undertake. We'll have to choose carefully which ones can be mounted at the present time.

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

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

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

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

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

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

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

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

DR. WINN-DEEN: Julio?

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

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

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

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

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

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

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

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

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

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

Debra?

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

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

DR. WINN-DEEN: James?

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

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

(Laughter.)

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

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

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

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

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

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

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

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

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

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

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

DR. WINN-DEEN: Other comments? Debra?

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

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

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

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

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

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

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

So it would be his view that the scientifically and public health responsible thing to do, whenever you do that kind of study, is to unblind the marker so you can make sure that even if you have this blockbuster drug, it's not a blockbuster because of the power in the subpopulation.

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

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

DR. WINN-DEEN: James?

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

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

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

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

(No response.)

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

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

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

MS. CARR: Sure.

[BREAK]

DR. TUCKSON: Behind schedule. Shame on us.

Well, what I'm really concerned about is that Emily is going to have to wind up having to chair the last half hour of the meeting because I've got to be someplace to give some kind of major keynote. I'm trying to be the bad cop so Emily doesn't have to be at the end. So I'm saving her again, so you'll think she's the most wonderful person and I'm the bad person. So that's the way it works.

All right. We're going to go ahead and roll up our sleeves and drill deep and let's see what happens.

DR. WINN-DEEN: Turn to page 1 of your yellow pages, entitled "Background Information on Proposed Approaches."

PARTICIPANT: This is the second page 1?

DR. WINN-DEEN: Yes. The other page 1 has some other title on it. I just think it's useful to have all the stuff together in one place.

So we clearly already had quite a bit of lively discussion about translational needs. So I don't know that we have to reiterate that except to say that there are things going on, but I think from the sense of the committee that maybe we don't think there are enough things going on or that there are still some gaps in the translation process.

So we had introduced a couple questions in this section. Do the current research activities meet the needs identified by SACGHS, and how should research to determine the effectiveness of pharmacogenomic-based drugs and tests be conducted, especially in a diverse population?

We had, under proposed approaches, that we should promote inclusion of diverse populations in pharmacogenomic studies and that potentially health care organizations could become more actively involved. I think what I heard from the discussion before the break was that there's a more fundamental gap there which is that we really need to be funding the final phase of translational research. So once we understand that there is a genotype that could be associated with a drug response or affecting drug dose, that we need to take it to the next step, which is to actually develop the data set, which drives the clinical practice on drug dosing and economics.

So I'd like to add another potential recommendation in there, as well as opening the floor up for discussion on the two recommendations that are up on the screen right now on making sure that we include sufficient diversity and that we also try and reach out to the private sector to the health care organizations that may also have quite a big database of patients and outcomes that could be partnered with to develop the translational information that we need.

Let's take comments and questions. Debra?

DR. LEONARD: So, Steve, does the FDA even require pharmacogenomic studies? They don't. So in this first recommendation, I'm not quite sure what we're stating. You've got this friendly agreement they have to kind of provide it to you and there's a safe zone unless they find something. Then it's not safe anymore.

DR. GUTMAN: It's a matter of the state of knowledge. So if it's a valid biomarker that in some way has been linked to a product, I don't think you get to duck it. It's a question of how much due diligence and discovery might be required. But if there are known associations that impact the safety and effectiveness, then they become part of the review process.

DR. WINN-DEEN: Can I ask a follow-up on that? Isn't most of the diversity mandated by trying to make sure that the drug is tested during clinical trials in the total type of population that it would be used for? Isn't that really where it's mandated?

DR. GUTMAN: I'm not credibly familiar with all the nuances of drug review, but I know they, like us, have been asked to be more inclusive, to worry about gender issues, to worry about pediatric issues, to think about representative populations. So whether we're doing as well as we could, I can't say, but I know that certainly is part of our psyche to worry about things like that.

I think this is particularly unique because you do see very striking sort of population-specific differences that we might historically -- certainly in my shop we've not historically looked with quite the refinement that this might call for, and I suspect that the same might true in Drugs.

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

DR. LEONARD: Well, I don't know if this first recommendation or proposed approach makes sense.

DR. GUTMAN: Well, it does to the extent that --

DR. LEONARD: Yes, we want diverse populations included, but I'm not even sure the FDA is requiring pharmacogenetic studies to begin with to promote the diverse populations.

DR. GUTMAN: But if we weren't requiring them but a company came along with them and said that they want them because they'll help make the product more safe and effective or they'll help avoid toxicity or they'll help direct therapy, whether they're required or not, they are sometimes and they're likely more often to come along. So it strikes me that this is a matter of degree, not whether you should include diverse populations. This seems to me a safe recommendation, and it will apply to some products. It may not apply to all products because of the variable nature of what FDA might see or might request, but that doesn't mean this is an invalid request.

DR. WINN-DEEN: Yes. So should we just maybe word it a little differently so that we have the caveat when pharmacogenomic data is being utilized as part of a drug review, it should be gathered from a diverse population or a population reflective of the population that would be taking the drug?

DR. GUTMAN: If you have a more fundamental fault with the process, then you should say, and in addition, we think you should always look at pharmacogenomic data. But for when we do look at it, in those instances, it's just a no-brainer we should be looking at diverse populations.

DR. LEONARD: Well, recommending looking at pharmacogenomic data -- Sarah and I were having a conversation at the break that pharmacogenetics means several different things. One is it's getting the right drug for the right variant that's associated with disease, like Herceptin and HER-2/neu. You don't give Herceptin if there's not HER-2/neu amplification. The other is getting the right dose of a drug that will be effective, but you want to get to therapeutic and not to toxic levels.

That's a limited set of metabolic enzymes, transporters. We know most of the metabolic pathways by which drugs are metabolized, taken up, excreted. So in that case, you could ask every drug submission to say how is this drug metabolized, what are the variants, and do you have dosing recommendations. Sometimes with drugs, you don't know the genetic variants that they should be targeting, so you can't ask for that all the time. But the dosing area is fairly straightforward, I would think, unless they can submit data saying that we haven't been able to determine this or we can't or it's not metabolized by the regular pathways, or whatever.

DR. GUTMAN: Yes. I apologize I'm not more expert in drug either process, procedures, science, or regs. But my sense is that none of this would be alien to drug reviewers. I actually think these would be questions they would be quite interested in asking, and they probably would ask to whatever extent they thought was appropriate. So what you're asking for is something that we either already probably ask for or it certainly strikes me as things we should be asking for, perhaps with increased vigilance as this field emerges.

DR. WINN-DEEN: Gurvaneet and then Cindy.

DR. RANDHAWA: We have got a couple of issues here. One, I'm not quite sure if it's that simple to get into a straightforward dosing algorithm based upon whatever variant, metabolizer, or transport or

genotype we have. If you look at what condition the drug is being used for, and there are other pharmaceutical agents being given, drug interactions become an issue, perhaps a major issue, which may not be there in the drug trials to begin with. So I think there has to be a caution as to how much specificity FDA can give in its labeling advice for drug and genotypes.

The second issue I just want to clarify is here it says diverse populations without specifying what diverse populations mean. To me, genetic diversity is not the same as what Steve had mentioned about elderly population, younger population, and even the way risk is defined, it's more geographic inheritance rather than genetic inheritance. So can we have a little bit of precision of that?

DR. WINN-DEEN: It seems to me that if we're talking about genetic testing, it should be genetically diverse rather than age diverse. I think we could probably add that clarification.

MS. BERRY: I was wondering if there was something that we could put in a recommendation -- or maybe the group had already thought of this and rejected it -- that would go a step further and either provide an incentive for companies to conduct these types of analyses and provide this kind of data. I mean, you can do the hammer approach or the carrot approach, and there are pros and cons to each. If we feel that there isn't enough of that back-and-forth and submission of data, is there something more we would like to propose, or do we think the status quo is okay?

DR. WINN-DEEN: Yes. I guess part of what we still don't have -- I think the drug manufacturers would like clarity for how to design their clinical trials because this is a long process. It's probably a year in design and then two or three years in execution and another year in review and comment from FDA. So the better you can do the design up front, the less issues there are to discuss with FDA on the other end.

So I clearly think that the FDA can play a leadership role in helping to guide the way trials are designed. So I think that's our opportunity through HHS to really influence it. We don't control big pharma or little pharma. For that matter, we don't control private industry, but we can influence the way things are done to provide better medical outcomes.

I think FDA has been working to have two different categories: the "validated" biomarkers where, if you know that your drug is involved with one of these validated biomarkers, you're supposed to include it in the trial, period; and the exploratory research that might lead to discovery of a new biomarker, and that's part of this voluntary data submission. They've been really actively encouraging companies to do both kinds of studies, not just the mandated ones, but also the "maybe we'll find something" kind of studies.

I don't know what else we can do through HHS to encourage that. If people have other suggestions, I'd be happy to hear them and consider putting in some recommendations.

DR. LEONARD: I very much like Steve, but I'm wondering if we don't need someone from FDA Drugs because Steve is basically from SACGT and the carryover of the oversight issue and everything. The testing is one aspect. I'm not saying get rid of Steve. I'd like to keep him. But maybe we need someone from FDA drug review, I mean, Steve's equivalent on the drug side.

DR. WINN-DEEN: We've had Felix here.

DR. GUTMAN: I'm certain you can find someone either to join or to attend as appropriate. They're not trying to hide. Maybe they are. No, I don't think they're trying to hide. I think they would actually probably have found this discussion interesting.

DR. TUCKSON: Do we generally put ex officios on any of the subgroups?

MS. CARR: Yes. There are a couple people from Drugs on task force.

DR. TUCKSON: So we can informally ask Steve, would you please be the conduit and say that we would like on this subcommittee the right person from FDA other than you?

DR. GUTMAN: Yes.

DR. TUCKSON: That's just a formal deal which we will transmit formally. Thank you.

DR. WINN-DEEN: Joe?

DR. TELFAIR: I have both a question and (inaudible) on the answer. But it's a little bit different than the current thread. It's for number 2. It has to do with number 2. If we're ready to move there, just let me know.

DR. WINN-DEEN: Is anybody else commenting on number 1, or are we ready to move on?

(No response.)

DR. WINN-DEEN: All right. You're on, Joe.

DR. TELFAIR: Okay, thank you.

The idea of diverse populations was clarified. I wonder if we can also clarify health care organizations. Is there already a list of ones that most people would recommend, or is it something that we really need to be clear about, given the thrust of this recommendation?

DR. WINN-DEEN: I think what we were thinking when we wrote that was to involve folks outside of HHS like a Kaiser Permanente that's a big health care organization that manages lots of patients, has lots of data. They actually have done a bunch of studies on utilization of genetic tests and what makes sense in their practice. So those kind of organizations I think is what we meant when we wrote this.

Do want us just to say private health care organizations?

DR. TELFAIR: Just operationalize what you mean. I think that would be really helpful in order to be able to better understand what the recommendation is about.

DR. LEONARD: Also, we can only make recommendations to Secretary Leavitt.

DR. WINN-DEEN: I think we were trying to foster public/private partnerships.

DR. LEONARD: Well, but maybe we need to recommend to the Secretary that he could involve and explore mechanisms for encouraging or involving, but I don't think we can ask health care organizations to become actively involved.

DR. TELFAIR: That was it. Thank you.

DR. RANDHAWA: Perhaps you have another recommendation coming, so this may be premature. But regarding active involvement of health care organizations, they're already collecting data routinely. It's mainly claims data to pay bills. But all health care organizations want to get paid, so they do collect data, which is accessible to researchers.

One of the issues that we really have is genetic tests in particular, but lab tests as a whole are not really well represented in the claims databases. So what we are lacking more of is an infrastructure modification rather than the lack of ability or interest from health care organizations to capture the data.

So I don't know if you were thinking of having a separate recommendation on improved infrastructure or data infrastructure which then can have data available for researchers, or is it going to be a separate activity of health care organizations actively doing prospective studies independent of routine data collection?

DR. TUCKSON: Well, two comments.

One, let me, just as I answer that, revisit something that we just heard in terms of responding to Joe's point. It is true, Joe, that our recommendations are to the Secretary. I do think that we have taken the opportunity on more than one occasion to raise issues that are within the public domain that we would sort of think are important. So it is that we could legitimately say in the body of the report, while recognizing that the Secretary doesn't have control over it, the committee is interested and would be hopeful that a certain constituency reading this report might be stimulated or motivated to voluntary action on their own. So you can get that in. I wanted to make sure that everybody continues, even though we are being disciplined about recommendations. We are talking to the American people and you can do that.

One thing in terms of your comment is that you may find fertile ground in this then in being able to link this to the Secretary's issues on health information technology. There is a lot going on in terms of collecting and synergizing laboratory data with claims-based data in a more interactively dynamic way. Without getting into the granularity of that, there's a lot there. Companies like ours do that and many others are. So the idea of a common data platform that would allow that activity to be able to be a foundation for this kind of activity would be something that would be in the Secretary's domain.

DR. WINN-DEEN: It's my understanding that the CMS codes for tests allow you to report a test for reimbursement under certain codes that reflects what that test was, so that we should have some kind of database of what the testing that's actually going on is. It's not just lab tests without any further description.

MS. AU: I think it's on page 4 under infrastructure, the electronic medical record, collecting the data. That I think you put in the recommendation already. It's under infrastructure, point number 4, middle of the page down. So it is there.

DR. WINN-DEEN: Right. One of the things that I know that has been happening within the CMS coding for molecular genetic tests is going away from just having a procedure code that says sample preparation or whatever to having a little dash after that that indicates the actual test. What was the sample prepared for? What the test was? So in the past, it was difficult to track which tests were which, but we should be able to do that now more properly going forward.

Did you want to comment, James?

DR. ROLLINS: Yes, I'll make a quick comment on that. It is true that laboratory testing is something that CMS is trying to get a better handle on, but if that laboratory test was performed in a hospital and it was part of a DRG, it may be difficult to capture that. Tests done outside the hospital are more accessible.

DR. WINN-DEEN: Okay. Because it's just billed under the DRG and that's, I suppose, too even for private insurance. Is it not, Reed, that under DRGs, all the stuff that's done is just under there and you don't really see the granularity?

DR. TUCKSON: Right. That's the challenge.

DR. WINN-DEEN: All right. So maybe there's some infrastructure that can be built somehow even for DRG-related things.

More comments about translational needs? I think that we came up with some comments, in addition to these two, about wanting to encourage the funding of translational studies through NIH funding mechanisms. So I'd like to add that. We discussed that previously. We'll get some better wordsmithing than what I just said. Whether we should go to the encourage special additional incremental funding or just to encourage that each of the institutes within NIH should strongly encourage their groups that are developing the RFPs to consider making sure that there's translational medicine going on in all of those areas and not just leave it to PharmGKB or the National Institute of Medicine to do things, that each institute should be looking at it within what disease areas they are responsible for.

DR. TUCKSON: Well, I think I'm influenced by something that Francis said, and I want to make sure I understand how to do that. The idea of translational, as you said, bounces off the walls there. I'm saying this for debate not because I think I know the answer.

I think I'm a little concerned about if we were to recommend new funding streams because I don't think there's much practicality there. We barely got any money in the NIH as it is.

But I think that if we could find a way to sort of say that within the prioritization of the use of resources at NIH, we're saying this is important, we think it makes sense, and that within that, we think that such and so and so should occur. Can you help me with that?

DR. WINN-DEEN: Well, I guess I agree with that, that I don't think we should go back to Congress and say, you must give us X millions of dollars for this particular purpose.

My concern is I don't want to see other agencies within NIH saying, someone else is taking care of that, because this really crosses all the borders. So I'd like to see each agency charged with looking within their purview, within their things that they have to do in translational medicine -- and I assume that all of them have a charge to be doing something -- that they should consider pharmacogenetic things as appropriate for funding in their translational medicine component.

Does that seem like a rationale way to do it? Because I'm afraid that what will happen, Francis, is that everybody will say, well, that genetic stuff, that's Francis' job, and it will all have to come out of one or two agencies rather than being spread across all of them.

DR. TUCKSON: Good point.

DR. COLLINS: So I think if you're going to make such a recommendation, it would be good to be very explicit about what kind of studies you're talking about. Translational, of course, covers a vast array of applications. Pharmacogenetics covers a reasonably vast array.

What I heard people saying earlier was you would like to see more effort in prospective trials of pharmacogenetics to see whether those are, in fact, cost effective and avoid toxicities and failures to respond to drugs that are already on the market because I think we heard earlier that the drugs that are in development, this is hardly what NIH is going to be doing, this is what the companies are going to be doing. So if you could be fairly narrow in the definition, I think that would help people understand your intent.

DR. WINN-DEEN: Do you think it's a good idea to try and encourage all of the institutes to have a look at this and at least start considering it and incorporating it? This is, from my way of thinking, a little bit in our mandate to teach others to not think that genetics is this exceptional thing, that it needs to be just pigeon-holed in one or two places.

DR. COLLINS: I think many of the institutes, maybe not all, are already thinking about this and looking for research opportunities. I don't think pharmacogenetics is either sort of relegated to one or two support systems or considered to be really esoteric stuff. But this, undoubtedly, would make an impact if this were perceived as being a very high priority.

Again, I'll just remind you that unless you're going to ask for a special appropriation, by saying this is a high priority, you're saying something else is not.

DR. WINN-DEEN: I mean, each institute has to decide on their own --

DR. COLLINS: They do.

DR. WINN-DEEN: -- what that relative list is. You do that every year anyway. Right?

DR. COLLINS: We do.

DR. WINN-DEEN: Comments?

(No response.)

DR. WINN-DEEN: I'd like to move on to the regulatory issues. So we've gone through a number of these things particularly in our discussion after Steve's talk today.

We had identified specific needs of wanting to see better coordination between the research and the regulation. I think the pharmacogenomics data submission is a really good step in trying to coordinate that and make it less scary for pharma companies to actually do the research. Obviously, that also helps with incorporation of pharmacogenomics into the early stages of clinical trials.

Number 3, guidance is needed on how and when pharmacogenomics will change labeling practices. That seems to me to be the biggest gap today in terms of both pharma companies and their potential partner companion diagnostic companies really understanding what the process is within FDA to look at some data, look at a drug and change the label.

So I would like to ask that at some point FDA consider publishing a guidance or an informational kind of white paper that would just help those of us that haven't done it and even probably some of the people

who have done it really understand what the FDA is thinking about, what are the criteria that they use. Is it only severe adverse events? Is it optimization of response? What are the criteria that would cause you to put something in a label and at what point does a test have to be, I'll call it, commercially available either through a reference lab or through a diagnostic kit. Are there some criteria or some circumstances under which a reference lab test is not suitable, where it has to be an FDA-approved test? So to just provide some information on those things back to the community. That to me seems like it's still a gap where we could ask for more information.

Are there other things that people are concerned about? We have this one that's up here that was something that we had also talked about within the committee. Again, this would be helpful in that whole labeling thing. At what level do you say that you need testing? If it's a 1 in 1,000, you need a test. If it's 1 in a million, you don't. You can live with the risk. So I think this question that's up here is a subset of that whole discussion of how and when do you get a test incorporated into a label.

Are there more things that people would like to see in this regard?

DR. LICINIO: The adverse reactions I know go into two major groups, the kind of common and not so severe ones that, you know, it's nice if you can avoid them, but you know nobody is going to die of them. But the most troublesome are these that are really severe, this kind of idiosyncratic reactions, anaphylaxis, the Stevens-Johnson syndrome, and things like. They tend to be very rare because otherwise the drug will not be approved.

So to get enough cases to do a meaningful study, you really have to foster like a national registry or national collaboration because not any one center can do it. The way that research is funded now, you have to apply for your own grant to do your own thing. But I think that if some comment could be made about maybe creating like a national registry or database for severe reactions that then could be the --

DR. WINN-DEEN: Is there not already an adverse drug --

DR. TUCKSON: There actually is one, yes. Steve, you may not know everything in the FDA, but there is a new effort, isn't there, to create a registry?

DR. GUTMAN: Yes. Well, there's actually always been a program called MedWatch and there's always been both an obligation and a voluntary reporting mechanism there. There's reorganization in the Center for Drugs to provide more independence to the group that is looking at adverse drug events, and there is some change in resourcing and systems. So the agency actually has taken its notoriety very much to heart and is trying.

Actually there are some corollary things going on in my own Center for Devices that are following suit trying to --

DR. LICINIO: But just a question. In this case, the different people, let's say, from different parts of the country report to you, but they're not in touch with each other. They don't know who the others are. So there is not like a real kind of a network that the people who had the reactions --

DR. GUTMAN: Yes, that's correct. There's not a listserv or an information sharing pool.

DR. WINN-DEEN: So it sounds to me like what we need is sort of a follow-up mechanism or a loop-back so when MedWatch identifies something that there is then a way to immediately get out and study those people?

DR. GUTMAN: Oh, no. You may argue that it could be more effective or different, but that exists now.

DR. WINN-DEEN: So there's a way right now through MedWatch to go out and get a genetic sample, for example, from each of the people who had an adverse reaction?

DR. GUTMAN: That I don't know, but there's a mechanism for doing all kinds of things, including contacting companies, contacting hospitals, contacting laboratories, directing inspections. I don't know about collecting and running samples. I would think that that certainly is within the purview. It might be challenging operationally.

I think that the regulations are strong enough to allow a fair amount of flexibility. So the question is making them operational for an event like that.

DR. WINN-DEEN: Francis?
DR. COLLINS: So the AERS database is a potentially valuable source of cases of this sort, but it certainly is not an easy or uniform solution, given that it is voluntary.

DR. GUTMAN: No, no.

DR. COLLINS: Well, okay. What percentage of adverse drug events are actually reported?

DR. GUTMAN: Now you've got me.

DR. COLLINS: I think estimates are maybe 10 percent. So it's not capturing a lot of what happens.

While it is possible, I know from talking with folks at FDA about this, to get back to the individual who suffered the reaction and try to get a sample, it's not straightforward. You have to work through the reporting physician who may or may not be interested in helping out. There's no easy mechanism to provide a carrot for that help to appear.

So I think the suggestion of trying to tap into other means of discovering across the nation adverse drug reactions, and particularly working with some of the HMOs that have large clientele and computerized systems for tracking such events, is really an idea whose time has come. I don't think if you're really interested in looking at post-marketing, rare adverse drug events, that AERS alone is going to do it.

DR. TUCKSON: Well, let me just say that I will give you the name of the contact off-line since I've got to be careful. One of my subcompanies is a company called Engenics, and they actually collect and send that information, post-marketing adverse events, based on a database of well over, I think, 70 million people. Anytime any new drug comes out, they monitor that pretty much and then feed it back to FDA and others. It's called I3, and so without doing any further conversation about it, I'll do it off-line and you can go to them independently and find out about that.

So I think Francis is right on the money there.

Julio, I think you hit it and there are things that we can do.

DR. WINN-DEEN: So, again, we should have some recommendation to deal with both the HHS database through MedWatch, as well as through any private databases that we have for surveillance, to try and identify things early and get people enrolled in a study that might lead to understanding how that event came to pass. I understand there are huge issues when you only have 10 adverse events and

500,000 SNPs you might want to do on a HapMap-generated whole-genome association. There are some real issues in never finding anything, but we should at least try and put mechanisms in place.

Gurvaneet?

DR. RANDHAWA: I was curious. I agree this is an important area to investigate. As part of the benefits and harms calculation, if we can figure out using pharmacogenetic testing how we can reduce harms, that's wonderful.

The flip side of it is we can also use pharmacogenetics to identify non-responders. Is the committee thinking of making a separate recommendation for that, and if you're thinking of creating a national registry of outcomes -- adverse events are essentially outcomes -- why can't we have efficacy and effectiveness outcomes also to see where the drugs actually didn't work. That might also save a huge amount of resources that may have been spent not very well.

DR. TUCKSON: Do you see that sort as collected at an aggregate level for study purposes for precision on the advice and guidance of how to use the drug?

DR. RANDHAWA: Absolutely. I think that is what I was alluding to also before lunch in prospective studies. If you can get a sense of is there a (inaudible) there before we do that, then we can go ahead with work conditions, what genes, what drugs.

DR. WINN-DEEN: I think one of the conundrums that the community has faced for some of those things is that some of the genotypes are not 100 percent predictive. So what do you do with someone who's predicted to not be a responder, but you know that 30 percent, let's say, of the "non-responders" actually do respond. Do you withhold the drug from them? There are some ethical issues that you get into when it's not a real yes/no kind of response from the genetic analysis. So we also have to somehow deal with those issues as well because I don't want to get in a situation where you're denying someone a drug that they might benefit from.

DR. RANDHAWA: I agree, but usually we have more options than not. So you can always think of changing the class of the drug or a different drug. It's seldom the case that there will be just one drug that has to be given or not to be given. But I agree with your point.

DR. WINN-DEEN: So you're saying that really, instead of not giving them a drug, you'd give them a drug that they're more likely to respond to than the one that you were considering. Choosing among a set of three, which is the best one for this patient, is a different story than saying the only option is drug 1 and you're not going to get it. So we just have to keep in mind all of those ethical scenarios as well.

I think that we can move on. The next section was on incentives or barriers to companies to co-develop drugs and pharmacogenetic tests.

Certainly one of the issues is coordination of the timing, and I don't know that even if Steve comes up with an improved version of the companion diagnostics white paper, you're still going to have that issue of how do you know soon enough to get a test validated and ready to go in the clinical trial.

But we can potentially deal with this issue of, I'll call it, the disconnect between the orphan drug designation and the orphan device designation where you have an orphan drug whose threshold is quite a bit higher than the 4,000 cases that puts you in the orphan device category. So I don't know if FDA, within your knowledge base, has had any internal discussion about how to rationalize that disconnect.

DR. GUTMAN: If there have been, I'm not aware of them.

DR. WINN-DEEN: So that's an area where I think we could potentially ask for FDA to look at whether, if something becomes an orphan drug because it works only in a small set of patients, that the test that goes with that drug also gets the same orphan status and be allowed to get through, rather than having to face the much more difficult threshold of 4,000 tests a year for 4,000 individuals a year.
I think the concept of using orphan drugs, orphan devices to deal with subpopulations of folks who are, let's say, a small minority population but that could have great benefit from something is one that we don't want to ignore, if there are things out there. Again, to the comment that Gurvaneet made earlier, that if the power of your overall population efficacy is driven by just a small number of people who really respond well that are mixed in with the total, you really want to understand that difference. Is it really 60 percent of people respond or is it that 10 percent of people really respond? And if so, can you make the financial incentives for making a drug and a test for that drug attractive enough that the private sector will go for it?

Changes to the Orphan Drug Act is getting into Congress, I'm afraid, and not just HHS. That's true. Right?

MS. CARR: Well, you could suggest that the Secretary propose changes.

DR. WINN-DEEN: My biggest thing here is that if we're going to put pharmacogenetics or some kind of a subpart in that gives orphan status to one part of the health care, it ought to give orphan status on both sides. I'm not quite sure how to say that better. I think that was really what we're trying to do, and we also want to make sure that the small subsets of people who could really benefit from something aren't denied it because it's just financially unattractive for companies to commercialize.

Any discussion on that recommendation?

(No response.)

DR. WINN-DEEN: Moving right along, the next section was on infrastructure, and we've talked a little bit about infrastructure already in terms of needs for what's out there already, what kind of surveillance would be useful. The question, I guess, before us is what additional infrastructure do we think is needed, if any.

So we had under this infrastructure a recommendation to incorporate basically genetic analysis in both the drug approval and the post-marketing process and, as such, encourage more wide utilization of pharmacogenetics. So I think this goes back a little bit to what we said in the earlier part about funding translational studies. I don't know. Maybe those two recommendations can be merged together there.

Any other comments on how we should deal with that issue and recommendation?

(No response.)

DR. WINN-DEEN: Good. We might get out of here early.

DR. TUCKSON: If there's no comment on it, is it because we don't think it's a priority or you like it?

DR. EVANS: I would echo what I think was just said, that perhaps this should be rolled into that first recommendation. My personal view is that this is perhaps the most important thing.

DR. WINN-DEEN: All right. We'll note that.

Direct-to-consumer. There obviously is a little bit of work going on in this area already. It's not directed just at pharmacogenetics, but more broadly the FDA and FTC are working together to look at false claims for any type of genetic testing. I don't know if there are additional things that we want to do or if we want to, as is outlined on page 6, address the fact that things are already happening. We've already written letters to the Secretary. As a result of that, we're pleased to see that there is this joint task force in place between FDA and FTC.

I guess the next thing that that task force could be doing -- and we can discuss this -- is whether we want to try and encourage them to provide some kind of advice to consumers, things to watch out for about genetic tests in general and maybe pharmacogenetics. I'm a little less concerned about pharmacogenetics because it's not that likely that they're going to be able to get the drug that their test told them to take without seeing a physician.

DR. LEONARD: No, but they could change their own dosing.

DR. WINN-DEEN: Yes, that's scary.

DR. LEONARD: Yes, it is scary.

DR. WINN-DEEN: So, Steve, where do you guys stand on actually getting to some consumer alert kind of thing? Would it be helpful for us to say that that would be useful, or are you doing it anyway?

DR. GUTMAN: We're working on a consumer alert, and it is not immediate but it's in the very near-term future. So once it's published, if you decide that more is needed, then perhaps at the next meeting, you could say, well, that's a nice start, but here's what you should do. But you probably should wait and let us get it out.

Once we get it out, we will try to -- I imagine FTC has mechanisms for distributing those things. We certainly will link it every place we think appropriate and try to get in Reader's Digest or something. It pays to advertise. I would at least let this run its course. I think it's a first step. Whether it's enough or not is a different question.

DR. WINN-DEEN: So then I think we probably should just change our paragraph basically that indicates that that is imminent and that we're in support of that concept, and if we have any further recommendations, they'll come. Do you think that will be out before the June meeting?

DR. GUTMAN: yes.

DR. TELFAIR: Can I say something?

DR. WINN-DEEN: Sure, absolutely. Joseph.

DR. TELFAIR: Just on the other side of the consumer alert part, we could as a committee look at the composition of the alert itself. But I'm just wondering. Do we also have an obligation to make sure that there's an understanding on the other side related to that and that's something maybe on our list of things to do as follow-up to get -- I'm not quite sure how to word this. So I'll just say it and then maybe someone can help me word it.

I'm just concerned that the consumer side of the consumer alert be involved in the process of --

DR. WINN-DEEN: Right. So we have some stuff as we get to education, where we talk about consumer education. Is that what you're talking about, making sure that they understand, if they saw the words "pharmacogenetic test," even what it means?

DR. TELFAIR: Yes. If we already are covering that, then never mind.

DR. WINN-DEEN: Yes, I think we have some things coming up in the education part of that to address those concerns.

Agnes?

MS. MASNY: Just another point that we had already discussed on the other one about the regulatory issues of when something should be included in a drug label, that maybe just a consideration of when a consumer alert should go along with something that's going to be in the drug labeling.

DR. WINN-DEEN: So if a drug label changes, should a consumer alert be put out by FDA or whoever to people taking the drug already.

Do you guys have any kind of policy on that for when it changes?

DR. GUTMAN: We have an extensive system of alerting. I think it is more directed at the physician than at the patient unless it's an over-the-counter product, in which case we would probably be quite interested in reaching the patient.

Again, I don't have enough experience to know whether that would be perceived as an incredulous burden or a wonderful opportunity. I just don't know.

DR. WINN-DEEN: Other comments? Go ahead.

DR. TELFAIR: I'll say this and maybe repeat it when we get to that. The recommendation is to make the information more consumer-friendly, but I'm just wondering also if there should be just a specific comment related to coordination of that information because if consumer alerts come out intermittently, then there needs to be some way that whatever efforts are being put into making it more consumer-friendly or more user-friendly, that it's coordinated with the alerts as they occur independent of whoever it comes from. There needs to be some level of coordination. So I would expand the recommendation a little bit to make that because I think that if we did that, there's a degree of assurance that goes with that.

DR. WINN-DEEN: Do we need to make sure that our consumer alert is the first thing that comes up when you do the Google search so that the consumers are getting that information before they get the other marketing information on direct-to-consumer?

DR. TELFAIR: It makes sense that you would have that, to have some kind of clarity on that because the marketing could be very well done, but understanding leads to more informed use.

DR. WINN-DEEN: Sure.

Debra?

DR. LEONARD: It will be interesting to see what your alert says. But you require drug labels. When we develop an in-house developed laboratory test, you require labeling on there to say what it is. Can there be labels required on these websites that meet your alerts and standards?

My concern is if you alert a consumer that they should take this information to their physician who's giving them the drug so that that physician can make appropriate dosing decisions, then those physicians aren't going to know what to do with it either. You can tell the consumer not to change their own drug dose or not to stop taking a drug based on pharmacogenetic information, but they're going to want to do something with it. And probably the only recommendation you can make is for them to go to their physician who's giving them the drug because they know the other drugs that they're on and how those may interact. But most physicians aren't going to know what to do with pharmacogenetic test information.

DR. GUTMAN: Yes. No, I think that point is well taken. I think that we had as a view making this user-friendly and actually doing, I think, what you're suggesting, alerting people not to start self-adjusting meds and to talk to their doctor. I don't think we actually had as a fundamental precept here that we would actually give their doctors brains.

(Laughter.)

DR. LEONARD: You don't have to give them brains, but you have to give them dosing information, which is what's lacking and it goes back to this ultimate --

DR. GUTMAN: Well, but you have to realize that some of this information is being generated and there is no dosing information because some of this stuff actually isn't -- well, I want to be kind, but some of this stuff is just too bizarre for words.

The problem wasn't that we didn't want to go after them. The problem was they couched their advertisement in very clever ways and made it very hard to posit a risk. Whoever they hired were very good legal or advertising staff, and they made it very difficult for Matt and very difficult for FDA to be able to find the kind of smoking gun that would allow us to take stronger action. So this consumer advisory is a second choice. It's not a first choice.

DR. EVANS: Just parenthetically, I think the bigger risk is one that is out of the purview of the FDA and that is that what is really gaining momentum in the lay world I think is the whole idea of individualized medicine, and there's a whole cottage industry of snake oil salesmen now selling things like nutraceuticals and that type of thing based on your DNA analysis. You can send in a cheek swab.

DR. LICINIO: Face creams also.

DR. EVANS: Yes, right. You name it. Spas do this, et cetera.

So that's a bigger issue that goes beyond pharmacogenomics, but pharmacogenomics is one subset and is much more regulatable and much more tractable than that. But it's something that in the future the committee might want to think about.

DR. WINN-DEEN: Well, I think we actually have looked at that, and that's part of what FDA and FTC are surveilling. So, again, to the comment that was made earlier today, if you see any gross, just total lying in advertising kind of things, please bring them to the attention of our liaisons to FTC, to FDA, to Steven and Matt, and they will incorporate them.

DR. GUTMAN: Again, I'll recap the history that when we started looking, what we think may have happened -- maybe this is delusional and we think we have more might than we do. But we started going on websites using computers that were identifiable as FDA computers, and the websites started to change and disappear. Now, that doesn't mean they didn't crop up elsewhere. But, in fact, we spent a great deal of time preparing what we thought was a great case for Matt, and when we went to do the final check, it was gone.

DR. WINN-DEEN: Self-policing, right?

I'm going to try and move us along here so that we can get through all of this stuff.

The next section was on coordination of efforts. We certainly have had a lot of discussion about the continued need for coordination of efforts among agencies and even potentially with groups outside of the U.S.

Apparently there has been some discussion about the appointment of a genetics czar or coordinator. I personally don't recall that discussion, but it was there somewhere, I suppose, since staff has this in here. Do we feel that the field of pharmacogenomics requires some particular assignment of a person within HHS to act as the coordinator, or does HHS generally find its way to creating the right kinds of subcommittees and things? I'm going to ask the people who are within HHS whether they feel like they sufficiently coordinate among themselves or if they would find it helpful to have someone who was a designated go-to person to just make sure things are happening.

Oh, sorry, Francis, did I take your --

DR. LEONARD: He doesn't officially have the title of czar.

DR. WINN-DEEN: You know, being a czar is a double-edged sword because the last czar, as you know --

(Laughter.)

DR. COLLINS: Be careful what you ask for. Look around the government recently and tell me where is an example where the appointment of a czar has actually led to a good outcome.

So are we not better off to try to continue this effort to coordinate between agencies by people who are already committed to this, rather than somehow making that somebody else's problem, which will then provide, if anything, a disincentive to the agencies to try to work together because it's somebody else's responsibility to see that happens? So I have to say I wouldn't be very enthusiastic about this idea.

MR. DANNENFELSER: I second that. I think there's a tendency to layer on too many new layers of bureaucracy in some of these cases, and I think you want to limit the amount of times that you call for that. So I would agree.

DR. BRADLEY: I would agree. I think from my perspective, which is very short within the government, but still, I think there has been increased cooperation. We certainly have been working with a number of different agencies on EGAPP and other things that were initiatives within our office. So I think there's quite a bit going on actually between the agencies.

DR. WINN-DEEN: Well, I'll take that as one we can strike from our list.

On a personal perspective, the things that we've asked from this committee to see coordination on I think have all resulted in coordination of activities. And I think if we can continue to highlight bringing together information so people know what's going on in other agencies, my perception is that a lot of times it's not a desire not to cooperate, it's just a lack of knowledge that there is something going on in parallel. So I'd like to encourage this committee to continue its mandate to encourage that kind of public exchange of information so that all that stuff is out on the table.

Part 2 of this recommendation or potential recommendation --

MS. MASNY: Emily, the only question that I have on this about the coordination and that was the international aspect. Is there any need to include that in what's happening in HHS?

DR. WINN-DEEN: Does anybody from HHS want to talk about that? It seems like we're getting that when we need it, but it's more on an as-desired basis.

DR. COLLINS: I think actually the lines of communication are pretty good in the field of genetics, maybe in part because the Genome Project itself was international with major involvement by six countries. The HapMap was itself international. Six countries were involved in that as well. At a scientist-to-scientist level, a lot of connections were built and strengthened that are going to be quite durable. And I think at the agency level, the U.S. agencies learned to work quite productively with their counterparts in the U.K. and in Japan and China and Canada, Germany, and France. So we could always look to see how this could be better, but I don't think at the moment that this is a major problem.

MR. DANNENFELSER: To the extent you might have to involve the Office of Global Health Affairs at times in this, the director of that office already has a Global Health Policy Core Group that involves most of these agencies within HHS. So I think you already have a mechanism there, that you could get it on that agenda, if you had to. So I don't think you need to bring something new in. I think there's something there. You just have to tap into it when it's needed.

DR. WINN-DEEN: All right. On to clinical practice, factors influencing uptake. So, great, we have the data. Now can we get it to become part of clinical practice?

There are a lot of educational efforts underway I think. We've made our comments as a team on that. We've sent a memo up to the Secretary about the need for continuing genetics education in general. And I certainly would view that pharmacogenetics is not an exceptional subset. It's part of that learning how to use genetics information to better manage patients.

I guess the question we have is whether we think that there's an easier path or an easier message maybe to carry forward, less scary message associated with teaching people about pharmacogenetics and maybe more immediate applications than the perceived "specialty" of dealing with people with genetic disease, which is a much smaller percentage of the population.

Certainly when we get to the genetic component of common complex disease, we'll be dealing with, pretty much, anyone and everyone. But the whole field of genetics has sort of evolved from this real specialty where you just deal with the monogenic kind of diseases that are pretty rare but highly penetrant.

This is sort of the middle case of trying to get genetics out into society more broadly. Is this a good way to start doing more broad education so that when we do have the common complex disease stuff, that things are already in place in terms of people have heard the words and maybe they've even had a test at some point to help personalize their medicine?

So the question is, do we need to anything more than what we've already done, which is to encourage that genetics education continue to be funded pretty much all the way through K through post-grad and even continuing medical education for health care professionals who are done with their formal schooling? Or is what is going on already, as part of the overall education sufficient?

Any comments? Debra?

DR. LEONARD: Well, I find this a little problematic because I'm not quite sure what we'll be telling them, when we are missing this final step of you do the test and then this is how you change the dosing, if it's a dosing pharmacogenetics that you're talking about. If it's a right drug in the right patient like Herceptin and HER-2/neu, that's relatively easy to educate about.

But I'm just concerned, given that a number of us have said that the highest priority should be these prospective outcomes trials, funding of those, so that we know what to do with this data clinically, that if we start advertising, and yes, you can have the test done, and no, we don't know what to do with it, it's not going to be a very good education advertisement.

DR. WINN-DEEN: Yes. So I'm not sure we should be advocating advertising anything until we have all our ducks in a row. I think the question is just as these ducks come into focus, one after another, each one of them offers an educational opportunity to help people learn. So we have 2D6 and Strattera. We have UGT1A1 and irinotecan. We have TPMT. We have the warfarin story. We're starting to get maybe one or two stories a year coming into play where things are moving beyond the experimental and into more of the "routine." So should we be encouraging, as these things move into that realm, that each one of those is an educational opportunity?

Chira, and then James.

MS. CHEN: I think for the public, it's a little bit too premature as an educational opportunity, but definitely for the physician, especially if they're going to be prescribing these kind of services, or not prescribing, they are going to send the sample to do these kind of services, I think they should know what they're about and they should be trained how to make this kind of decision or talk to somebody to make a better decision. For just the general public, it's just too early in the game for doing that.

DR. WINN-DEEN: James?

DR. EVANS: Yes, and I would echo that. I think about HER-2/neu and Herceptin. Frankly, educating the general public about it is, in many ways, kind of silly because it's applicable to so few people. On the other hand, educating physicians and providers about it is incredibly important.

My feeling is that once the ducks are in a row and once efficacy has been established and we have good studies, which, of course, is an earlier recommendation, that number 8 is a great recommendation because I think it's true. I think that there are fewer stigma and potential ELSI kinds of problems with pharmacogenomic data, and therefore, it's a very good issue that we can sink our teeth into. We can educate and we can help the medical establishment roll out something that is not particularly threatening and is useful. It's low-hanging fruit.

DR. WINN-DEEN: So if I understand basically your comments, the education would be first to the physicians and then allow the physicians to educate their specific patients that would benefit from it and do it in a more targeted way in that way, rather than trying to do any kind of generalize public education at this point.

DR. EVANS: Yes. I don't think the public will feel cheated if they aren't educated about drugs that most of them will never use.

DR. WINN-DEEN: But are you watching the Lipitor commercials?

DR. EVANS: Yes. According to many people, it should be in our water. Everybody should get it.

DR. WINN-DEEN: I think the drug companies are out doing a little bit of education for us as well.

There are comments down at this end. Gurvaneet.

DR. RANDHAWA: I think it's an excellent recommendation. My only question is who does the education and at what stage. Part of the "who" is we all heard about the evidence should be there, the ducks should be in a row before we do the education. To me, that means there should be some sort of a professional society or organization that has a guideline on that area, and then that guideline can be disseminated. So if it's an oncology drug, there's the American Society of Clinical Oncologists or some specialty society, or even if it's a general practice, there's the American Academy of Family Physicians, American College of Physicians.

I think we need to get a process in which, once the evidence is there, there's a short time line in making evidence-based clinical guidelines. EGAPP is doing a very good job in making some progress there, but that really is what we need, buy-in from professional organizations at the beginning. And then who does the crafting of the message can be done in concert with them, not independent of them.

DR. WINN-DEEN: Agnes.

MS. MASNY: I was going to say something very, very similar to that and then actually ask Linda regarding the EGAPP project, whether there will be some type of education process with the findings of what you have from your pharmacogenetic study.

DR. BRADLEY: Yes, it will come out in several different forms. Obviously, there will be an evidence report from the EPC, the Evidence-based Practice Center, and a publication that will come out that, and then there will be recommendations that come from the EGAPP working group.

In addition to that, we've spent a long time talking about how those sort of technical and maybe not very applicable to the general population messages get translated and sent out. We're actually working with some folks to talk about how to do that.
So, yes, we do plan to do that. I couldn't tell you exactly what form that's going to take at this point, but it's definitely needed or the messages will be lost on a lot of people.
DR. WINN-DEEN: So our next recommendation really is very similar to this, about recommending mechanisms to make the PGX information more user-friendly and likely to be accessed and used. So I think we probably could roll those two things together and talk about this mechanism of determining utility, having it go to the appropriate clinical groups for recommendations, which then educate their physicians, who then educate their patients, and sort of doing this trickle-down educational approach, at least for the near term until it becomes so widespread that everybody should just know about it because eventually something is going to come up that they need.

Joe?

DR. TELFAIR: Well, earlier, remember the thing of the reverse of the consumer alert?

DR. WINN-DEEN: Right.

DR. TELFAIR: Wasn't this this recommendation, which is number 9, something that was referred to as a way to address that as well? So if we combine the two and you combine it as you have laid it out, what does that change?

DR. WINN-DEEN: Well, I guess the question that we had is to what extent can you expend energy educating people who aren't going to ever find this relevant in their lives. So I think the point that several of the people have made with regard to how to deal with public issues, is at the point where they are going to be engaged, they also need to be educated. I agree with that. The question is just, I think, a matter of mustering resources. Can we afford to create educational campaigns, beyond just the basic incorporation that genetics is a part of your life, into all of the education, K through whatever. Can we do targeted campaigns for pharmacogenetics? I think what I've heard is that we think it's not time to do a broad consumer campaign on pharmacogenetics at this time or to recommend that.

We have a few more recommendations to get through, so I'd like to try and move along.

In terms of the physician, can we get recommendation 10 please? Again, this comes back to how do we get the information the practicing physician needs to make it relevant to their clinical practice. That includes having an understanding of how to identify what patients might benefit and then knowing what test to order and then knowing what to do with the test result when they get it.

Steve, you said that most of the drug labeling changes, when labeling changes come, that there's a system for educating physicians. This might be a good time to just clarify what you know about that.

DR. GUTMAN: Well, it would depend on the nature, but it could be as much as an actual mailing if it's a significant enough alert or concern. The physicians here must all get these. There is, of course, a tendency to throw them away and not read them.

(Laughter.)

DR. GUTMAN: But I'm sure no one at this table does that.

I would imagine that more subtle changes, ones that aren't substantive, probably are put in the labeling without the same level of alert. So I think it's a matter of risk management and degree, but certainly significant changes the agency actually attempts to leverage through the drug firms. It's the drug firms' responsibility to provide that information. If the drug firm seems unwilling, then the agency is happy to help.

DR. WINN-DEEN: Right. So I can definitely see in the detailing of a new drug, if there's a test required, that the pharma rep is going to teach the physician all about the whole thing, hopefully, that they need to order the test, and then they need to order the drug because it's the greatest thing since sliced bread. So I can see how that happens.

Do you understand how it happens when there's been a label change so new information about an existing drug --

DR. GUTMAN: Well, I would argue that, again, it's a risk-based stratum. It would be the same thing. If the label change was a weak one, then I think there would be less incentive to make sure that everybody

got the word. If it was a really significant labeling change, I actually the agency would create some kind of communication plan collaboratively with the drug company to try and get the users to get the word out.

FDA has actually a lot of risk communication strategies. I don't know about Drugs, but I know in Devices we have lists of ob-gyns, list of pediatricians. We'll actually develop targeted mailings based on what subpopulation of the health care professional community we're trying to reach.

I'm not sure that just because a drug is not new, that there aren't people who are detailing or who are selling it. So I think that there probably are very complex considerations taken as to how you would do that.

But certainly I know and love the people in Drugs, and they're just as passionate about their products as I am. So I'm certain that if they made changes that they thought were relevant to the safety and efficacy profile of the drug, they would be very concerned with trying to get that message out.

DR. WINN-DEEN: James.

DR. EVANS: I would echo what you said about the inadequacy of our current ability to get through to physicians about changes. I don't think that's the fault of the FDA. I think it's probably the fault of physicians. But it's a huge problem.

I would add, for whatever it's worth on this, to explore the potential for existing and novel partnerships. I think this whole realm that we're dealing with in genetics calls for novel ways of getting information to physicians because physicians have a singular fright of things genetic, and they really feel like they don't understand it well. It's not going to be enough to mail them things because they throw them away.

DR. WINN-DEEN: Chira and then Debra.

MS. CHEN: Could I make a recommendation? Every year, or I don't know how often, doesn't a physician need to take classes? And this could be part of the classes.

DR. EVANS: They can take whatever they want.

MS. CHEN: Could it be put as a requirement that you have to take certain ones?

DR. LEONARD: The only way would be to have pharmacogenetic testing included in the recertification process because everybody has time-limited licenses now. So that would be the only way.

MS. CHEN: That would be great.

DR. LICINIO: I know this is an investment for the future, but another suggestion might be to talk to the American Boards of Medical Specialties and request that at least some questions on pharmacogenomics be included in the boards and that be part of the topic that people have to know to pass their boards.

DR. WINN-DEEN: Gurvaneet?

DR. RANDHAWA: Yes. I would suggest another and perhaps a little bit more efficient strategy would be, in terms of where we're moving with health information technology, e-prescribing, pop-up alerts, whether it's through your PalmPilots or on the computer screen, that as and when new pharmacogenomic testing becomes available with adequate evidence, that this become a part of the algorithm or protocol for giving the drug. When the physician is to prescribe warfarin, there's a pop-up screen that says have you

done a test for such and such genes. So it should be a part of our new ways of disseminating information and making it part of the clinical protocol.

DR. WINN-DEEN: I'm afraid that a lot of the physicians who might be the most recalcitrant are not using any of those electronic-driven things.

DR. EVANS: I would agree with you about the pop-ups and all, but working perhaps through the formularies. There are many agents that formularies at hospitals have some control over. It might be reasonable to envision ways that when a physician prescribes agent X, Y, or Z, that there's a reminder, a call, an e-mail, whatever, about the need to do testing.

DR. WINN-DEEN: Debra?

DR. LEONARD: I hate to lump, but couldn't 10 be included? It's very similar to 8 and 9. It's basically educating. So can they all be combined into one recommendation?

DR. WINN-DEEN: Well, I think what we'll try and do is we'll try and listen to all this feedback and then reconstitute these recommendations in a way that makes sense, whether it's one, two, or three. Each of these little statements was really designed to engender some discussion and feedback so that we could get to what the real things we want to say are on each of these subjects.

Cindy?

MS. BERRY: Related to this last point, though, I know, for example, the American Heart Association has developed, in conjunction with agencies and with the cardiologists, a variety of groups, these clinical decision support tools for the treatment of cardiovascular disease and stroke, heart attacks, and whatnot. So these start out as hospital-based programs where they can develop a very specified, specific treatment protocol for a patient and there are prompts on the computer that assist a doctor in coming up with those things. Then there are patient education materials that are generated upon discharge and whatnot.

I'm wondering if some of these groups, like the Heart Association and others, and those that are engaged in clinical decision support tool development, could weave in pharmacogenomics in whatever it is they develop. I think also these things might have been developed in consultation with JCAHO and some of the other accrediting agencies. So maybe some of those agencies could be involved in some way that would facilitate or encourage the integration in clinical practice.

So that's just one area, and since heart disease affects so many people, diseases like that might be a good place to start. I don't know how it exactly weaves into the recommendation, but it's a little twist, anyway.

DR. WINN-DEEN: I'm going to try and skip ahead a little bit here. The next couple sections I think we've actually already covered in fairly good detail. The next proposed approach 11 dealt with ways of representing populations in clinical trials and assuring diversity in the clinical trials. I think we've already gotten quite a bit of feedback on that subject. So I'd like to skip over that one.

Proposed approach 12 again had to do with how to remain compliant with current regulations. I think we can work on a recommendation that basically says people should be compliant with current FDA and NIH guidance, depending on what kind of study they're running.

We have about 12 minutes by my watch. So we've got a few more recommendations here.

One thing I'd like to discuss a little bit is the section on liability and its influence on standards of practice, and particularly since Cindy is here today, to get a little bit of a view on how much we think the liability factor might be a driving force in leading to adoption of these kind of tests. At what point does something "become standard of practice," and do physicians leave themselves open to malpractice suits if they don't implement something? I don't know if there's anyone else that has experience or expertise to lend to that discussion, but it certainly seems to me that it's an aspect of what drives physicians to adopt new things that we can't really overlook.

So is there anyone that has any light to shed on that subject? Agnes?

MS. MASNY: Just a comment about liability driving the practices. For irinotecan, in one of our noon conferences, they brought up the discussion about this testing for the UG2A1A. Most of the physicians there felt that because it was already on the label, then they were obliged to provide the test because if they didn't provide the test and if someone had a toxic reaction, then they would be liable for not providing it, since it was already on the label. So I think it was just as a comment that this is a very clear concern that once something appears on a label, then physicians are liable then to provide that test.

DR. WINN-DEEN: Cindy?

MS. BERRY: The crafty trial lawyers will come up with new and innovative ways and use this. If someone does a test and they determine that an individual patient is not a candidate for a particular therapy because of some gene or whatever and the doctor explains that and they don't give them the therapy and there's a bad outcome, some lawyer could say, well, you should have given the therapy anyway. And then if they do give it to them, and there's an adverse event, it's sort of a no-win situation.

Then somewhat related to this, these controversial cases that are coming up about obstetric screening and testing and whether the child has some kind of anomaly or problem and if they misinterpret the test or they don't give the test and they did a wrongful birth. There are things that are popping up in the legal system that are going to be difficult to manage.

So I would say that we should do our best to recognize that that's out there, but we shouldn't let it thwart what we think is the best practice of medicine that would help deliver the best, most appropriate patient-centered care. But we should always keep in mind that there are these people out there trying to take advantage of science and, unfortunately, create some weird incentives in the delivery of care. We're always going to have defensive medicine because of it. So, unfortunately, I don't know that we could shield the medical profession from that. We just have to be cognizant of it.

DR. WINN-DEEN: So do you think it's important for us to, for that reason, perhaps err on the side of conservativism in terms of when things are put into an FDA -- I mean, from a patient point of view, you might say, put it in as soon as you think there might be a reason to test, and from a legal liability, you might say, put it in after you're really, really sure. Somewhere in there is the right time to put it in depending on what you're thinking about, what's driving you.

I hate the idea of health care being driven by lawyers, but I recognize that there's a certain reality to that.

MS. BERRY: Well, then linked to all of it is the coverage issue as well. The threshold for a health plan or for a federal health program to cover something may be different from what FDA might initially recognize or acknowledge in a label. So that would affect whether a patient receives certain tests and a certain therapy.

And then do we exacerbate existing disparities when maybe a health plan won't cover it or the Medicaid program won't cover whatever it is? A patient of means could still pay for it out of pocket and obtain it, but someone who is on a health program, government program, and they don't have the means, they don't receive that. Then what are the problems there?

DR. WINN-DEEN: Right. Well, access to good health care is, I think, one of our overarching issues that we have to deal with here. I think part of the incentive for developing pharmacoeconomic arguments is to look at the overall episode of care and understand that, hopefully, if a test costs more up front, it also leads to a lower overall cost because you get to the drug treatment more efficaciously, earlier, or whatever. But those kind of studies, which are needed really to justify making sure everything is covered all the way through, are sort of long in coming.

MS. BERRY: But is the label the place for this, or is it more in the technology assessment coverage arena?

DR. WINN-DEEN: So I guess maybe we could highlight that there is and remains a disconnect between FDA approval of a test and FDA changing of a label and coverage and reimbursement. Those two activities happen as separate evaluations, and until they're linked, there will be these disconnects on access.

I think we certainly brought that up during the coverage and reimbursement discussions, and it's clearly enunciated in that report, but maybe we also want to make sure it's in this report as well, as one of those overcoming-the-barriers things. I think we have something on that in the overarching issues.

Martin?

MR. DANNENFELSER: I'm not remembering the term, but I remember when we were going over this coverage and reimbursement. Aren't there some threshold terms with CMS in terms of this? And I'm just wondering how that relates to what Cindy is saying, that perhaps the fact that it is in the label, that there is a medical indication or whatever, a medical basis for doing such a test might then give CMS reason to cover that test for people or whoever might need it.

DR. WINN-DEEN: Well, I think that's all part of the evaluation. I'll let James talk about what the threshold is.

DR. ROLLINS: In terms of threshold? In terms of what? Sensitivity or?

MR. DANNENFELSER: No, no. Whether CMS would provide reimbursement.

DR. ROLLINS: Well, currently CMS only pays for diagnostic testing, and a patient has to have signs and symptoms of a particular condition. If a patient has a family history of a particular disorder and if the patient does not have signs or symptoms of the disease, then they won't pay for it because they consider it's screening or preventative. Even though the FDA may say that this test has been shown to be effective for diagnosing X, Y, and Z, as I say, if the patient doesn't have signs or symptoms of it, Medicare will not cover it.

DR. LEONARD: Where does pharmacogenetic proper dosing testing fall into that arena? If a physician is determined that a patient needs a drug and there's a label on there saying that these certain genetic variants predict proper dosing, where does that fall in CMS's realm to pay or not pay?

DR. ROLLINS: As far as I know, Medicare does not address the threshold for proper dosing, but it does acknowledge that if a patient has, like for example, TPMT, from what I've been told, yes, because a patient does have signs and symptoms of the disease, this test can be used to monitor the patient's condition, to determine whether or not the patient is getting a toxic dose or an insufficient dose.

DR. WINN-DEEN: Gurvaneet?

DR. RANDHAWA: Being neither in CMS nor FDA, I'm probably the best place or worst place to make this comment. If you look at the criteria, FDA looks at safe and effective. If you look at CMS, it's reasonable and necessary. So there is no way you can ever get 100 percent concordance between these two. That is how Congress mandated it and that's how the agencies are carrying out their missions. So I think there's a fundamental issue there about the evaluations that are different in the two agencies.

DR. WINN-DEEN: Right. So I guess what we need is these translational studies that demonstrate both improvement in safety and/or efficacy and that it would be reasonable and necessary for a patient to have that test in conjunction with taking a specific drug. So maybe when we do these translational studies, we should really consider both of those aspects in the study designs and try and deal with both those issues.

James?

DR. EVANS: I guess you can postulate that anytime somebody is going to be getting a drug, they're showing signs and symptoms of a disease, or they wouldn't be getting it. So does that mean that these tests would be paid for then, I mean, in the same way that TPMT testing is paid for?

DR. ROLLINS: I would hope that the patient would get the medication when it's most appropriate, when he had the disease, but I can't guarantee that all the time. But as I said, if a patient is having signs and symptoms, then it's considered a diagnostic test and it would fall under that.

DR. WINN-DEEN: We're going to have Debra and I believe one more comment to the floor, and then we have to wind up for the day.

DR. LEONARD: One more aspect of liability is if you do a pharmacogenetic test that is for a particular dosing of a drug, it has implications for dosing of a lot of other drugs. So what is the liability there if you have information about the potential to overdose someone with one drug and you give them another drug that's metabolized the same way and you don't take that into consideration? So at least we're talking about using pharmacogenetic test information almost as an allergy alert, where it's posted everywhere and everyone would know it, and the pharmacy would have a list of drugs that are also affected by the same thing. So there's another way to look at the liability issue as what about the liability of other drugs or drug-drug interactions.

DR. WINN-DEEN: Right. So this comes back to how do we put things in electronic medical records so information isn't lost over time and you can truly do a genetic test on someone once in their lifetime and have that information retained with them.

Are there any other comments?

(No response.)

DR. WINN-DEEN: If not, I want to thank everyone for their very productive feedback, for all of your thoughts and words, and for really helping the task force to move this report on to the next level.

We will resume tomorrow morning at 9:00 a.m. in this room.