Review of Oversight Charge

DR. TUCKSON: All right. We're actually trying to start. We're ready to begin, if you can close the door.

Here's what we're going to do. We're going to ask Greg, who doesn't know that we're asking him -- Greg, so we're going to ask you to come on up to the table for a sec, Greg, if you could, and help us out a little bit.

Those of you for public comment, we're going to come to you in a minute, but we're way early here. So we're doing good.

If you look on your schedules, after we come back from lunch, we are scheduled to go into our discussion on the oversight of genetic testing. We were very pleased to have gotten the guidance this morning from Sheila Walcoff. So what we want to do is -- can we put up on the slides the summary of those recommendations? -- look at the charge that we got this morning. So what I want to do, to make sure that we have a focused oversight discussion when we come back from lunch, is I want to just review with you those recommendations, those charges to us, to see whether or not there are any questions or if we have any issues there as we start to look at things going forward. I asked if Greg would be here in case we had questions that we wanted to ask him about helping us to understand intent or anything that was unclear.

So if you look at what was presented, that we develop a comprehensive map of the steps needed for evidence development and oversight of genetic and genomic tests to improve overall health quality. So if you start out with we're being asked to describe the existing pathways that examine the analytic validity, clinical validity, and clinical utility of genetic tests and then to define the responsible organizations who are, in fact, responsible for those three things -- let me stop there.

Is there any question or issue about our taking up this descriptive assignment? So it's really describing or documenting the existing pathways that examine analytic validity, clinical validity, and clinical utility and then defining the organizations currently responsible for each of those.

So, Muin?

DR. KHOURY: I mean, that's a very good question. Actually this job should be made much easier given all the work that's been done over the past few years. So it's just pulling out these old documents and looking at them.

DR. TUCKSON: Right. So that's a defining of reality.

Andrea?

DR. FERREIRA-GONZALEZ: When you say organizations, can you be a little more explicit?

DR. DOWNING: That would be from sponsors to federal regulatory agencies, research organizations, and professional organizations. That may be different, depending on where you are in the development of evidence from analytical validity to clinical utility or cost effectiveness, if one wanted to even go to that extreme. We didn't include that last parameter in there.

But there are conduits of information aggregation and analysis that we think could be useful if lined up in terms of the responsibility and the questions of what evidence is needed, in some cases

resources, whether it's well-characterized specimens or reagents that would enable a certain test to be performed. We would like to see some sort of a categorization, if you will, of the types of information that are needed at various steps.

DR. TUCKSON: Kevin, you look puzzled. Oh, Steve, go ahead.

DR. TEUTSCH: This is very clinical. Is this limited to the clinical issues, or are we also looking at things that relate to the public health and population health utility of these tests? Or is this limited to the clinical side?

DR. DOWNING: If you could clarify the distinctions on how you would see those being separate, maybe it can help with the answer.

DR. TEUTSCH: I think we understand how it could be used for prevention at the individual level, but to the extent that one is going to have this information out there and you're going to have the genetic information that's going to be used for population health that may be related to toxic exposures in the environment or recommendations for nutrition policy -- or you could think of a lot of things where these tests might have population health impact or for specific ethnic groups or geographic groups.

DR. TUCKSON: I guess, Steve, the question would be -- and Muin, I think, has some thought about it, I'm sure. But I'm just trying to make sure I understand your question. I don't think that this first question that they're raising is -- it's simply any test for whatever purpose has to have some utility and validity. So I think if you sort of put it in that context, regardless of the ultimate application of it, does this thing work ultimately is the fundamental question. So I think if you're saying that you can think of some tests that you would want to see -- tests that would be used at the level of population base, that you should, I think, think about putting that in this mix.

DR. TEUTSCH: I agree. Certainly what you're talking about deals with the analytic validity and the clinical validity. Does it measure what it's intended to do? It's really about the application. Is it limited just in the clinical sense or for population health management?

DR. TUCKSON: So in other words, you're taking a higher level view here for the minute, moving from the specific to an overarching thing, saying -- so let me just see if I can reinterpret your question, if I'm listening to you correctly.

You're saying should a generic purpose of the oversight of genetic testing be for clinical individual patient use and, in addition, tests that are used in population-based environments as well. Should it be that the oversight is both from a generic point of view? I think that, Greg, your expectation from the Department is, yes, it would be both.

DR. DOWNING: Yes.

DR. TUCKSON: Okay. So that's good.

So where I am now on querying the committee is I'm combining, as you can tell, the first and second bullets, essentially which is one thought in my mind. So, again, it is saying to us that they would like us to document and define the existing pathways for analytic validity, clinical validity, and clinical utility and define the organizations that are currently responsible for these activities.

What we've heard from Muin is his opinion that this is pretty much a fact-finding activity. There's a lot of work that's been done, and we've gotten the clarity from Greg that that would include almost all the domains of organizations that may be relevant to this, whether they're in the Academy, whether it is private sector initiatives, whether it's government regulatory agencies. It is to really try to lay out a road map that says here are all the relevant organizations and entities that are involved in this sort of oversight and definition of acceptability.

Are there any other questions on this first point?

DR. FERREIRA-GONZALEZ: We have heard this morning that the Secretary's office is actually looking very closely at the oversight issue within the federal agencies. I was just wondering, as we go through these different questions that cover not only the public sector but the private sector, how do you think we should focus our work on these issues since the HHS office is already looking at the federal issue? Should we just focus first on the private sector? I mean, what is your take-home on that?

DR. DOWNING: The bulk of the efforts thus far are looking at -- as you know, each of the agencies that play in this space with regard to genetic tests has a lot of different authorities assigned. And how those align and how they're applied, what are the intersections of them has been the focus of trying to develop more comprehensive understanding internally. One of the roles of the Department is to assure that the communications and interactions of various regulatory aspects and the deployment of their policies are clear and are understood by the other organizations and aspects of the duties that other agencies perform are done in concert in understanding of that. So our efforts to this point have been trying to, in an exploratory way, look to see where are those intersections and where do the authorities of one agency align or perhaps intersect or not in terms of gaps or overlap of particular policies and regulations.

One element that I would like to interject here also is on the aspect of genetic tests. Whether it's the performance of them or the ways in which the information is acquired and delivered to those that use it -- there are many different types of technologies that are evolving now. And I would think that looking historically at the documents from 2000 and 2001, I realize many people have probably moved on from the committees that worked on that. One aspect that may be of interest for this group is to look at specific requirements for different types of genetic tests, whether we're simply talking about PCR or complex, multi-gene array analyses and how the information from that is developed may have some differences in terms of the clinical validity as well as the analytical validity in how that information is developed.

So we would ask that the interpretation and defining of genetic tests take into consideration the methodologies, the types of information that are developed, how it's processed and presented as information or data to be utilized for clinical applications or in population-based health.

DR. TUCKSON: Let me make sure then. We've got a couple of issues here. I want to make sure.

On the first point, Greg, then as we look at putting together the map that has public and private sector initiatives that are involved in analytical and clinical validity and clinical utility, you're saying that even while the government efforts are going forward to look at its domain, we are to be looking at this comprehensively and pointing out from our map where those gaps are and that sort of thing. So I think that's the assignment that we're being given.

Secondly, you are saying that you want us to be sensitive to the methodologies that are deriving these tests and how information is processed and disseminated as subtleties that we should be thinking about in case there are issues that are obtained there. And that's something that we would sort of add to this first mix. All right.

So this is all what I see as point one. So it's the first two hash marks there I'm combining into one assignment.

Can we move the slides, please, to one next down?

Yes, Marc?

DR. WILLIAMS: One thing on the second bullet, and this is maybe a bit of language parsing. But you're using a term that's different than the one that's up there, and I think it's an important distinction. The second bullet says "currently responsible" which implies that somebody has actually taken responsibility. The terms you're using are "are currently involved with," and I think that's better language because there's a lot of this that's taking place in a very informal or ad hoc way as opposed to a formal way. And I think we need to capture all of that informality.

DR. TUCKSON: Well then, Marc, let's try to do both points and say "are involved with," and then as part of our recommendations, when we get to the recommendations part, "should be explicitly responsible for." So if somebody can capture that, I think Marc is on to something here. We want to say "are currently involved with."

When we get to the end of the exercise, it should be that we are making recommendations as to who should be accountable for, responsible for, and take it out of the informal, unless that informality is working as it should.

Could we move, please, to the slides? I'd like to skip down to the one that says "what new models or approaches for private solely and public/private sector engagement." Could you move to that one?

Yes, sir?

DR. TELFAIR: I apologize for interrupting, but you covered the first two bullets on that first one and you're deliberately not covering the last one?

DR. TUCKSON: Exactly, for the moment. I'm trying to make logic out of this, and because I'm not as smart as you, I can't do quantum mechanics and, you know, multiple permutations. So I've just deliberately lumped together what I see as one coherent idea, and now I'm moving quickly to a related idea as part of the first idea. I believe this question of what new models or approaches for private sector versus private/public sector engagement in demonstrating clinical validity and utility for developing effectiveness measures for use of genetic tests in clinical practice should be considered and why -- I'm trying to sort of see and sort of try to work with Greg here. I'm interpreting this -- and I may be interpreting it too narrowly -- to sort of getting to the point that Marc gets to around "responsible for." What I think this is getting to is you've got some of these things which can be -- this responsibility is government fiat, whether it's CLIA, whether it's FDA, who should be what. Some of this may be that you can work out responsible public/private partnerships and accomplish the goal. So it's not always done by government regulation. And I think what they're asking here is for us to think about a legitimate role for public/private sort of partnership as a solution to some of these problems.

So let me just ask Greg. Am I overreading the intent of this one or not?

DR. DOWNING: No. I think what we've been trying to do is to understand, much like was discussed earlier this morning, the use case scenario, is where are the information hand-offs, who needs what information to do what with. That has not been clear in some of the earlier meetings in terms of where does that information come from, how is it applied in the decisionmaking processes. And then from a standpoint of affecting clinical care or population-based approaches, what are the key analytical questions that have to be framed and answered in order to develop that information necessary to use the test and use it in a way in which there's transparency about the implications of their results.

We have seen recently published a number of models and discussions by other authors, not by members of this group, about what it would take in terms of organization, the science input, the medical input, the health systems input, in terms of the deployment of these technologies and the information necessary to make a process in which information continues to accrue. And there's refinement about the use of those tools and their applications.

So we don't have a concept in mind specifically, but we think that it's going to take more than just the federal government's role in defining a pathway forward.

DR. TUCKSON: So what I think you've clarified for me is -- the reason I wanted to engage this discussion as part of the clinical validity and utility definition was whether the challenge was more focused on the public/private partnership role for clinical validity and utility versus the appropriateness of the use of the test in clinical practice. I hear you emphasizing more the latter. It's more on the clinical use of the test and not as much on the former. Or is it both?

DR. DOWNING: It's clearly both. That's one of the intersections that we're trying to cross here. Where do those responsibilities currently fall and what are better ways to accrue that information as we go forward?

DR. TUCKSON: And I saw, Kevin, your hand.

DR. FITZGERALD: Just also for clarification, Greg, on this. So in the pharmacogenomics report, we also identified clinical outcomes as an important part of this whole sort of formula. Now, it's not in here specifically, but I'm presuming now you also mean that.

DR. DOWNING: I think that's certainly useful, if the committee can stretch to that point, to look at those efforts. Again, I think they're at various stages of technology development and their deployment. There's more and more to learn about that. If there are insights and there's expertise of this group to deal with that, then great. If not, certainly the evidence that we're really looking for more proximally related to analytical validity in the oversight of the test kits themselves, the materials that are brought in, the performance of those tests, those things are, I think, the prominent concerns of this committee that have been debated in the last few meetings that we'd like to try to get to in terms of more clarity.

But those longer, more distal aspects of it, I think if there are insights about bodies or authorities or ways to aggregate that information -- obviously we see the future of health IT facilitating that. That was one of the reasons why we were working on that aspect of it downtown. We would certainly be eager to do that, and I know that a number of the other agencies that are here today are also quite interested in those facets.

DR. TUCKSON: So let me do this then. I mean, I get you. The logic of where my head is then is what I think that we are being asked to do -- and you guys are going to need to track this here -- is on point one, this describing the pathways that exist now for analytical and clinical validity and clinical utility and defining the responsible organizations, the people that are involved and ultimately responsibility and accountability, as a co-part of that charge, it also includes to look at the appropriateness and need for public/private activities in this space. So it's basically saying let's look and see if there are some roles there once we lay out this road map for whether or not it's all government regulation, government oversight, but also the role of public/private partnerships in this regard. So just to that point, we're putting all that together as a bundle.

If we will now go back to -- while Muin raises his comment and also -- who's that?

DR. RANDHAWA: Gurvaneet.

DR. TUCKSON: Oh, yes, good. I always messed your name up. So that's why I said it that way.

(Laughter.)

DR. TUCKSON: You are from now on GR.

DR. RANDHAWA: I'm just G.

DR. TUCKSON: Just G., okay.

While we do that, I want to scroll back up on the slides back to the Joe Telfair, who won't let me get by the third bullet of the first slide. So that's where I'm headed.

Go ahead, Muin.

DR. KHOURY: Yes, I guess I just wanted to reinforce your idea before we get to this because those public/private partnership discussions have already occurred as part of the deliberations of previous committees. I think the clinical validity and utility of tests and their oversight, as it exists right now, would never allow for the complete type-proof, so to speak, of genetic tests seeping from research to practice. So there will always have to be this kind of public/private collaboration going on. I think we discussed it at length in previous committees.

So I think part of the existing pathways discussions could be the existing pathways plus the suggested pathways that were discussed in previous committees. So that leads you into, I guess, number three in terms of this.

DR. TUCKSON: Exactly. That's where I'm headed. You hit it right there.

Dr. G.?

DR. RANDHAWA: Thanks, Dr. R.

A point of clarification. I'm reading the words, and it says, "developing effectiveness measures." So is it developing new measures, or is it just collecting measures we already know and synthesizing them appropriately? I wasn't quite sure what the intent of that bullet was.

DR. TUCKSON: I think Greg will answer that. Let me just ask you to restate that again. Reask it one more time.

DR. RANDHAWA: Sure. I guess there are two subparts to that question. One is in here it says, "demonstrating clinical validity and utility for developing effectiveness measures." The two parts that I'm getting stuck on are "developing" and "effectiveness." So in terms of development, unless we're thinking of new measures, we already know many existing effectiveness measures. So are we developing measures, or are we just synthesizing and collecting?

DR. TUCKSON: This is a very important question. I do not think that the charge to this committee is to be concerned about the adequacy or how to stimulate more measures per se. It is the oversight of whether or not new measures are being developed or promulgated appropriately, that they are rational, that there's some accountability for the oversight of it. I don't think we're being encouraged to how do you get more stuff done, more genetic testing done, more tests. It's more of a sense of being clear that there is a relationship in science to the measures that are being developed and that they are connected to science so that the public can feel confident that, just as in the test themselves, there is someone who is involved, whether it's the public or private sector, in making sure that it's not just snake oil.

Now, let me just triple check that.

DR. DOWNING: Yes. We could substitute, in your parlance, the terms of evidence development, if you would like, to use in terms of how do we know that the test is providing the kinds of information that clinicians and health care providers and consumers want and need and can trust and reliably use and under what parameters is it useful in those conditions. If you're thinking about new ways in developing that information, that would also be insightful and useful to whomever carries on those responsibilities. I'm not suggesting on a technical or scientific level that we need guidance on -- I mean, the science should carry forward and the technology evolves. We're not looking for, you know, we need more specific ways to measure RNA and that sort of thing. Is that kind of to your point?

DR. RANDHAWA: Absolutely. So that helps.

The other part was the effectiveness. Are we considering efficacy as a part of effectiveness here, or are we focusing only on effectiveness?

DR. DOWNING: No, I would combine those two approaches. I'm giving, as Sheila mentioned this morning, some latitude to how this committee wants to frame its issues that way.

DR. TUCKSON: By the way, I did a poor job of introducing this topic and moderating it. I think that that last comment is extremely important.

I think that what we are, in fact, doing here is that the Secretary's office is trying to give us a sense of what they think they need, and we're trying to get clear here. When they say that they're giving us latitude, the Secretary's office recognizes that the committee has its own ego, surprisingly. This is a pretty head-strong group. And they're trying hard, I think, to say to us -- and I should have made it this way. They're not trying to dictate to us what we do, but we asked them how could we be most helpful. So you're right.

Within sort of the terms of latitude, I think what they're trying to do is to come back to us and say respectfully to the committee, if you want to know what we need to know to move this agenda

forward within the Department, here are the issues that are on our mind. And this conversation that we are now having is trying to get down to little more levels of granularity about what is it that you all really think you all need help on.

So Dr. G. raises an important question, which I hadn't fully understood. There is a subtly here that we're moving from the actual oversight of tests, which we have been fanatically on, to now introducing, in addition to the tests, the measures of effectiveness, which is sort of a step outside of our normal box, which is something that we're going to have to really start to think about whether we want to engage. I think that we've clearly got that in front of us. So your question actually has been very helpful.

So now, we're going back to bullet three on slide one. So far, we took the first bullet, second bullet, and this last thing, and we took half of whatever bullet this was down in the bowels of the thing and brought that up into one giant gemisch. A technical term, "gemisch."

Now we're moving to topic two which is the potential pathways to communicate clear information to guide tests and treatment selection by the provider. So what we've just done is to take the second half of the stuff we just went through with the public/private partnership stuff and we're now bringing that up and grafting that half to this.

So now we're saying we understand that we're being asked, as part of this one, to sort of talk about the role of public/private partnership, and that means the Academy and professional societies and who knows what in terms of being able to communicate clear information to guide test and treatment selection by the provider. So now I'm grafting that onto this number two.

Do we have any further comments around this number two in clarifying this goal?

DR. FERREIRA-GONZALEZ: Greg, is this where you think we can look at a different technology and how we could communicate clear information to guide test and treatment?

DR. DOWNING: Can you repeat your question? I'm not hearing.

DR. FERREIRA-GONZALEZ: You mentioned earlier that you want us to look at how we not only differentiate testing but also the different technologies, how you go about looking at the different technologies and relating that information to the physicians and how that gets interpreted and ultimately tested. So do you think this is, within this number two, I guess, something that we can address?

DR. DOWNING: So I think, as mentioned earlier, we're not looking for complete inventory of every test that can be done and categorized as a genetic test and then what's needed for this. But surely some framework of understanding particularly those cases where it's not just a positive and negative result, whether we're talking about something like PCR, but where there are cognitive and sort of interpretive skills and analysis that are needed and what levels of expertise and input -- how is that result interpreted and what is the information that's passed to whoever is going to be making decisions with it.

In reflecting on some of the earlier reports, a lot was focused predominantly on the test performance, and we think that still is a very important question. Is the test performed by the protocols in which it was done and the evidence supporting the analytical validity of that instrument or the reagents that are used to perform that test?

But I think, as we're moving into more and more complex areas, that what's new since some of the earlier reports are in those cases in which there's an interpretive side of this that's provided. How is that information gauged? What's the level of evidence that the test results are benchmarked against? And if that's utilizing other data sets and things, how is that performed and what are the cognitive capabilities that are needed to make the accurate determination?

So there, I think, perhaps may be some needs for expertise that might be on an ad hoc basis outside and beyond this group that would be important in informing those processes.

I think, again, just to step up to where we're looking down on all of this, that one aspect of it is that I think Joe is going on -- we found it particularly difficult to start from the very beginnings of when a specimen hits a laboratory or someone is going to be using it or a new method is developed, all of the steps they go through in terms of developing a piece of information that a clinician or a consumer or whoever is doing the test is making decisions about it. Lining all of that up and explaining it to someone in a layperson's terms is very challenging thing to do, and I'm not sure I can do it yet. That doesn't mean that there are others in the room that can't.

But these things in the past have been sort of aligned in pieces and chunks, and what we're trying to do is say where does the information flow go that guides this clinical decisionmaking. And ultimately in terms of the public health interest, that's what is foremost and of importance here.

So I think it's difficult for me, in looking at the kinds of cases and arguments that have been made this way. To do it in the abstract and just describing a genetic test doesn't help us very much if we're not able to put it into some context of saying here are the kinds of information that were accrued, here's how the tests are performed, here are the kinds of skills and knowledge base that are used to make an important piece of information, whether it's a number on a piece of paper that's faxed somewhere or put into some protocol that is able to develop numbers and probability statements. And then long-term-wise, I guess what we're trying to get to is a world in which that information is part of a clinical decisionmaking process.

So we're certainly not getting there yet, but all of those steps require different pieces of information to line up to make the assumption at the end of the pathway that that number has passed through all of those processes and it has valid meaning.

DR. TUCKSON: And it's something we'll discuss when we come back from lunch in terms of the oversight committee, but maybe one way to get at this is to actually take a few examples of case studies, and you sort of start from the beginning all the way through and you trace it and you sort of say, okay, what happens. So some real use case scenarios might be the way to get at it. I really like what you're trying to do.

Let me move quickly to the next slide and the very first one on the top of the page. I'm thinking now that what we might want to do is to make the first bullet -- the first dash there -- the very first question and put that at the very top of the whole thing and make that number one because, at the end of the day, that's the fundamental question. What's the point?

So it's like laying out what evidence of harm exists regarding genetics. Do we have any sense that there are real harms being done because of the gap? So I think it's important to identify what the real -- and I think if I understand the question, it is identifying either what are the harms or what do we think could be the likely harm that will exist through various developments of case scenarios. So we sort of say, okay, let me show you exactly that there's a hole that you can drive

a truck through that allows maniac test number three to be inflicted on the public, whether it has actually occurred or not. And I think we have to define actual harm examples and potential.

MS. BERRY: Just for clarification, are these all interconnected? To ask it another way, what if -- and I'm not suggesting we're going to find this at all -- we found there's no harm, no potential for harm, there are no gaps, currently regulatory schemes are --

DR. TUCKSON: Return to your homes. All is safe.

(Laughter.)

MS. BERRY: -- coming along, everything is great? You recommend that we still go to that third bullet under "general questions," which is what are the potential pathways to communicate clear -- I mean, are they connected? Do we have to find that there's harm and gaps and all of that to get to that, or is that a separate -- can I pull it out?

DR. TUCKSON: Great issue. I think the way that we would phrase that, if you think about where the committee is -- and we'll see what you meant. But I think, as I understand it, if you take the case scenario stuff and you drive it along, then you do have that issue still. It still exists, that middle point in your train. It still exists as an issue, and I would assume we would still have to do it.

DR. DOWNING: Right. I think this is all to the element of transparency of how information is gathered and used, and what you decide is safe to go out in the world today may change tomorrow. So we still need to know what are the processes to deal with new information as it unfolds.

I would like to address this harm issue. One aspect of this is really distinguishing -- and Dr. Collins used a number of examples in dealing with GINA this morning, underscoring the immense importance of genetic information in a lot of ways. How is that different than other kinds of medical tests? In the context for legislative purposes, genetic information is a very broad definition. We're going to leave you to decide how you want to define that, but in the context that the types of information that you get that have genetic origin is used for a lot of different types of decisionmaking processes, it seems a tenet to us that levels of risk and tiers of risk perhaps about the nature of the types of decisions that are made based on test results have some bearing on the level of oversight and the kinds of questions and evidence that's necessary in those circumstances.

So the aspect of harm doesn't necessarily mean that somebody has to be harmed in order for somebody to not be doing the analytical work. That sort of thing isn't what's intended here. It's trying to distinguish how are these types of technologies and the types of tests being performed here distinguishable from other types of medical tests. You know, CBCs. We're not talking about cholesterol levels here, I don't think, today. Again, we use those for population-based studies. What is it that's unique and definable about the types of genetic tests here that cause concern?

DR. TUCKSON: Francis?

DR. COLLINS: So I think this is a good discussion about exactly what is the point of that particular bullet. I guess maybe we ought to be a little more generous in terms of what we're looking for. We're not only looking for the evidence of harms or potential threats, but aren't we also looking for instances where public benefit has been slowed or limited, not that harms are

occurring, but that benefits are not accruing as rapidly as they might, just to put a more positive kind of view on it, but also to indicate that genetic testing in general, I think most of us agree, ultimately is going to be a public good? Of course, it could be limited if, in fact, it is used in inappropriate ways to cause harm. But not achieving the public good as quickly as it might optimally happen is also something we should be concerned about. So perhaps I'm just reacting a little bit to the language.

Now, maybe you will say, well, that's a harm if benefits are slowed, but it's a bit of a different use of the word than many people would assume where they think of somebody actually being injured. Here I'm talking about somebody just not benefitting because our process for oversight of genetic tests has, in some way, retarded the introduction of highly validated, highly useful tests at an affordable cost that the public can take advantage of.

DR. TUCKSON: But there's the challenge. You were rolling and then you got to the end, and you had to make 14 caveats to explain it. So I think we'll give Greg a chance to see what he means by it. But when we come back and chat, I think it's a provocative point, Francis. I fear -- and, again, we have a whole session this afternoon to talk about these things.

First of all, I like the philosophy that you're getting at here. I mean, we make it seem as if, again, genetic tests are something to be so scared about that, my God, oh, fear for your lives, all. The original way we got into this is pretty specific. It gave the committee a real chance to make sure, hey, let's just make sure nobody gets harmed.

Now, you're adding on something that I think is philosophically terrific, really complex to define, but still important. So I'll reserve the rest of my comment for that at the end.

But what do you think?

DR. DOWNING: I think Sheila addressed this earlier in terms of looking at the aspects that don't stifle innovation and the ability to apply technologies in new ways. I think that we see a lack of clarity and transparency at this point of having some stifling effect of whether it's commercial investment or academic investigators not wanting to really go into diagnostic development in some context because they don't know what the implications of the research will be. So harm is broadly defined here in the context of what are the implications of the results of not knowing or having that information.

DR. TUCKSON: Good.

Yes.

DR. EVANS: I just wanted to make a plea, if it's appropriate, for being appropriately narrow in this. And maybe that could be accomplished by just switching those two sub-bullets. I don't think that we probably as a committee are intended to address all of the harms that can result from problems with clinical validity, clinical utility. I mean, those are very much the same for problems that arise with the fact that we may be doing harm with PSAs and may be doing harm with whole body scanning.

I think it might be worth, if that's appropriate, defining in some explicit manner that we're looking at the types of harms that can result because these are genetic tests. Is that in the spirit of what you're getting at?

DR. DOWNING: Yes. I appreciate it. It really did not enter our discussions in framing these questions. There are many open questions relative to the appropriate clinical applications and knowledge, and you've mentioned a number that have public health implications.

I think that, at least from my perspective, there are other federal bodies that are dealing with that and you may want to describe them in a broad context, if the committee wishes to choose that path. But we don't expect that that's a necessary charge that you have to focus a lot of time and energy on.

DR. TUCKSON: So let's do this. Staff, follow me carefully on this here. I think this is what we want to do. We've been reordering the thing so we can come back and talk about this, when come back at the end of the lunch break.

By the way, public testimony is coming. Don't get scared. We got you.

Number one becomes describing the evidence of harm, and yada, yada, yada.

Number two now becomes genetic exceptionalism because we're focusing on genetics and the issue is what is it about genetic exceptionalism within the context of worrying about harm. So what's different about genetics is number two.

Then number three becomes the combined stuff we did on analytical and clinical validity and describing the responsible, you know, involved organizations and the point about the role of public/private partnerships in that regard. That all becomes number three.

Then number four becomes the notion of the models for choosing the right tests and making sure of the roles for the right choices and the right tests and all of that getting out there.

That then leaves us with asking Greg, in the last two minutes that remain, what do we mean by -- and I'm not sure I understand this point about the resource needed for proficiency testing. Maybe we could just hear a little bit about that and figure out where that goes in the flow.

DR. DOWNING: Thank you, Reed. You have a number of people here this afternoon that can, I think, address this question fairly well, and I think there's substantial talent here.

We heard, at least in the November meeting, I believe, and from others that the development of proficiency tests requires a certain amount of preparation, and how that's done in the community -- I'm not an expert in that and wouldn't want to profess to be able to explain all of the steps involved in that.

But having well-characterized specimens and the processes for splitting or sharing samples, what are the models for proficiency testing? And are there unique and common reagents or things that are used to test and provide common results from different laboratories performing those tests? I think we have not yet gotten a good handle on what that looks like, and particularly as new tests evolve and roll out, are those things commonly available and what are the implications of that on the laboratory for everything from costs to the availability?

It would be fine to set up a perfect framework, but if it's not going to work in the real world and those things are not developed and there isn't a commercial place that one can go to to get those reagents to do the testing, then what has been achieved by that?

So if there's a menu of materials and things that would be needed, again, in a framework that addresses different types of genetic tests, are those materials necessary to provide the kinds of analytical validity requirements, if those are available commonly, it would be helpful to know those.

DR. TUCKSON: So let me do this, staff. If you would, please, in the ordering, move that proficiency up to right before describing the potential pathways to guide tests and treatment selection by a provider? So, in other words, it comes right after the clinical validity, utility, yada, yada, yada. So once you've got all the clinical validity, et cetera, then you do the proficiency. Then from proficiency, you move to, okay, now you've got all this stuff done. Now it's going to be introduced into the world. Physicians and others have to select tests. What about the guidance there? And then you end up, at the end of all of this, with the last thing, which becomes, okay, the big drum roll is, da, da, da, da, ba, boom, what else should the government be doing to do its job. What is your conclusion about your guidance to government?

DR. DOWNING: One of the examples -- and this has been borne out in this committee previously, and then Kevin's report is the -- just back up and think about this a little bit more broadly now in the context of voluntary submission of pharmacogenomics data, for example, not selectively utilizing those tests, but in the context of what can be done to foster and enhance or bring the science forward by new models of developing the evidence and the scientific framework in which to do this. There aren't very good ways -- and that works right now -- to do comparative analysis of genomic tests, for example.

So we are asking this body, I think, to be creative and think outside the box a bit in terms of the methods and approaches that we don't have perhaps on the ground today that could be developed without a great deal of encumbrances.

DR. TUCKSON: All right. Bottom line, we'll resubmit this back to you and it will become part of the discussion that Andrea will lead us through. Of course, the committee had presaged some of these questions in their work. She will be creative at being able to interweave the two together in a logical and coherent, organized, and efficient discussion this afternoon.

MS. BERRY: Am I taking it too literally when the Secretary is suggesting that we put together a map? Is that purpose of the first three? And I'm going to mess up what Reed already did because the way you outlined the questions makes logical sense and I support that. But if our charge is also to put together some kind of diagram to map out these pathways and communications and oversight, is that something that was intended here so that we should separately consider that as a task? Or is just addressing each of these questions in a logical fashion what we need to do?

DR. DOWNING: We think a tool that would help visually and graphically explain and provide some transparency that my mother could understand it in some context, that there's an overview process that goes through and the technologies are developed and performed in ways that there's an information flow that enables her physician and her clinical provider to know the right information, anything that would facilitate that I think would address Joe's issues, as well as ours.

DR. TUCKSON: I think also, by the way, you will probably see -- I'm not sure whether the staff actually had a chance to do it.

I think, by the way, it's both, Cindy. It is laying out a grid, as I see it. I think staff has already taken a look at it that sort of graphically tries to lay out what's existing today, what isn't existing, where are the gaps so you can start to just sort of look at it and see. So FDA has this. Here's the

thing that has to get done and the FDA has this part of it and CLIA has this part of it. And nobody has this part of it. I think that map is key.

I think the second map we've just heard today is using the use case, the individual cases. So you take a map and you trace it all the way through. So it's a longitudinal map, a "walk through the woods" map, which I think is going to be terrific.

So I think those are great questions.

Let me stop here.

DR. McLEAN: One quick question of clarification back to point either four or five, depending on how you arranged the sequence. The potential pathways to communicate clear information to guide tests and treatment selection. Treatment selection really has not been a focus of the oversight to this point. How do you want us to conceptualize treatment? Management, genetic counseling, pharmacologic interventions?

DR. DOWNING: Yes, that's a good question. The context that a number of these tests are now being applied in the processes for guiding or at least anticipated to be utilized in making pharmacologic choices, but treatment is in this context also more broadly in terms of either wellness decisionmaking processes or others. So interpret the context that someone is taking a test and making a decision altering some process or health function as a consequence.

DR. TUCKSON: I really think that's a great question. I think that's a good way to conclude it.

Let me just make sure that I get it. I think what I'm hearing, what I'm animatedly excited about, is if you sort of, in some ways, start at the end and you say, Mrs. Jones received guidance that was significant to her health and life and/or that of her family as a result of some information.

Now, where did that information come from? Who made the choice of using that information? Was it the right choice? Was she the appropriate candidate to get that information? So that has to do with how it was disseminated and so forth and so on. Was the information that was given about her biological processes accurate? Was the test worth a damn, da, da, da, da? So you start working your way all the way through to the back chain. So I think that's really what we're trying to get at here.

DR. McLEAN: And then you've got outcomes measures that will naturally come in.

DR. TUCKSON: Yes.

Of course, you take the question -- I think it was Marc, or I can't remember. Again, it could be level of population, that in fact the entire Asian American population of Seattle was given such and such information. Was that relevant and right based on some genetic-based testing or information? I think that's the way you sort of work it through.

All right. We're going to have to rock.

DR. FERREIRA-GONZALEZ: Is Greg going to be here this afternoon so we can continue?

DR. TUCKSON: No. This is the last we get to hear from Greg. I'm sorry.

Marc, is it real quick?

DR. WILLIAMS: Yes, this is very quick. I just want to be explicit about something. A lot of what we've talked about are decision support algorithms, those sorts of things. I think we need to be explicit relating to oversight of development of those things because there's already been some talk in other venues of clinical support algorithms that are now being scrutinized under the rubric of a device. So relating to the last bullet, which is how would additional or revised government oversight -- I want to include maybe elimination of as one of the options, that it's not necessarily we're going to keep adding things.

DR. TUCKSON: So you guys are going to subpopulate this outline in your afternoon discussion. By the way, I have a feeling, knowing you, that you're going to augment the outline because you've probably got other things that you want to look at beyond that which the Secretary's office has asked for. You are not limited by what the Secretary's office is asking you to look at. We are informed by it.

As a conclusion, Greg -- and if you'll send it back to the Secretary and to Sheila -- we are just extremely appreciative to know where we fit into your efforts, so that we're at least being able to be responsive. Since we are the advisory committee to the Secretary, it's nice to know what the Secretary wants to be advised about. So we are pretty specific about that.

We may, in our wisdom, decide to augment and add more to it, but at least we're going to give you back answers to the questions that you have asked. It sounds like the committee is pretty well squared away on that point.

DR. DOWNING: Reed, I would just say we're agnostic about the manner in which this is prepared, whether it's a report or a series of workshops or conference calls and summary documents. There are some deliverables I think that we've talked about that would be helpful. I just want to underscore timeline is of some essence here, and we'll leave you to deal with that.

DR. TUCKSON: So what I think that means, Greg -- and even though we're rushing to closure here, I think this is important to slow down on. As you have been very engaged with us outside of the meeting day to day, we're going to have to give the committee members some sense of the timeline that you guys are rolling on. We understand your overall 600 days calendar.

The question will be to basically hear back from you, oh, by the way, there is an interagency task force meeting on, like, April 15th -- a bad day I chose -- and we're going to deal with questions one, three, and seven. If you've got anything for us by then, it would be enormously helpful to get it in. That's the kind of thing I think we're going to have to look for.

So the subcommittee is going to wind up being fluid and doing a lot of work by conference call and then you guys will join in as need be.

Thank you. You didn't expect to do that. So good job.