

Discussion of Final Recommendations (continued)

Facilitators: Reed V. Tuckson, M.D. and Andrea Ferreira-Gonzalez, Ph.D.

DR. FERREIRA-GONZALEZ: All right. Let's move right into the next section. We are going really move. Chapter 4, Recommendation 1. Recommendation 1 in Chapter 4 proposes steps to support and augment the CMS action plan in lieu of the CLIA genetic testing specialty. We revised Part A of this recommendation to call for CMS to require proficiency testing for all high complexity tests for which PT products are available. We did not revise Part B or C of these recommendations.

So, do we have any questions about this recommendation?

MS. TURNER: Just a reminder comment. With the change of "cannot be achieved immediately," there is a "may" before "cannot." I imagine that "may" should be deleted.

DR. FERREIRA-GONZALEZ: Thank you.

DR. TUCKSON: So this is back to the issue of the genetic testing specialty, which everything falls on. Could I just make sure I got the reason that we are not recommending the genetic testing specialty? Why did we decide not to do that?

DR. FERREIRA-GONZALEZ: Genetic testing today is covered under CLIA. There are specific personnel requirements under CLIA that fall under high complexity laboratory testing. In addition, it is kind of a moving target. Trying to put something that is an evolving field into a specific cubbyhole might be problematic down the road.

As we have already in CLIA specific issues to deal with high complexity testing, the personnel requirements, quality control, and so forth, we felt that this already covered that particular rule. So what we saw is that the only issue that was not covered for genetic testing under the current CLIA regulation was the proficiency testing. By making these changes to the proficiency testing, we actually solved some of the major concerns related to the lack of specialty and genetic testing.

DR. TUCKSON: Was that pretty much, again, the unanimous position of the taskforce? Is that where we are? Given that we have so many comments that were critical of this, I just want to make sure that I know how to assess the public comments on this.

DR. FERREIRA-GONZALEZ: Marc.

DR. WILLIAMS: Our starting point when we were first crafting this, I think, was really to follow the direction that SACGHS had previously given to support creation of a genetic testing specialty. But over the course of the time we discussed this, with input from our representatives on the taskforce and CMS. By really getting down to the points that Andrea brought up, which are what is the real issue and what do we really want to accomplish here, I think we recognized that if we fell back to "We just want you to make a specialty" that we would once again mire ourselves in the mud.

By doing this, with the support of our colleagues on the taskforce from CMS saying "We think that this is the way to go," we might actually be able to accomplish what we want to accomplish and avoid the problems that would be encountered in terms of trying to create an entirely new specialty.

SACGHS Meeting Transcript
February 12, 2008

I can't speak for everyone on the taskforce, but I think everybody was at least comfortable with that direction going forward. I don't recall anyone that stood up and said this is just absolutely unacceptable, although you are completely correct to point out that there were specific public comments that did go to this issue. We did consider those, but we ultimately decided there were not compelling enough reasons to redo this to ask for creation of a specialty.

DR. FERREIRA-GONZALEZ: Another thing to keep in mind is that, as I call it a moving target, what we were starting to see is what is a genetic test. It is not just what we have thought in the past, nucleic acid-based technology. Our definition is more broad and encompasses current specialty areas within CLIA.

So actually, the genetic testing cuts across current specialties that are listed in CLIA. Putting all this different genetic and genomic testing that is covered as a high complexity laboratory test and just fixing the issue of the proficiency test, then we can cover the majority of the issues that were brought up to us as concerns with genetic and genomic testing.

DR. TUCKSON: I guess it would be helpful for some of us, and we don't have to wordsmith it here, to nail down what the gaps are. At the end of the day, if you had to say, "We are agreeing that there are some key gaps. Those gaps are:" Is it possible to succinctly summarize the gaps?

DR. FERREIRA-GONZALEZ: Related to the CLIA specialty?

DR. TUCKSON: No. For a number of years CMS has been planning to address gaps in the oversight of laboratories that conduct genetic tests. Again, all of the gaps in the oversight could have been done with the addition of a genetic testing specialty. However, we are saying CMS has changed direction and is now addressing, again, these gaps. So, what are the gaps again?

DR. FERREIRA-GONZALEZ: Well, some of the gaps were not only the proficiency testing that we have already identified but how they were actually reviewing genetic testing laboratories. CMS has actually developed a plan to develop more guidelines for the inspections and how to inspect genetic testing laboratories. Maybe Judy Yost can fully talk about the gaps, too.

MS. YOST: I think it is very important to recognize that the majority of the issues that you are dealing with here are not covered by CLIA, first of all, at all. Secondly, to craft regulations, I think, as Andrea was indicating, for technology that is so dynamic at this point in time would clearly cause that little chilling effect that we talked about earlier and really limit and prevent for future development.

Instead, if you step back from that thought and look at, as Kathy Hudson indicated, what is it you are really looking for to do within that authority, you can get there from here. The only place that you would have to do regulation would be for the PT, which we have already committed and agreed to do because we could look at all the PT needs across the country, not just for genetic testing.

But you can get to personnel requirements through professional standards. You can get to quality control. There is a CDC group that is working on genetic testing quality control. Those recommendations can go into our guidance to laboratories. Believe me, anytime we place something in there, people do it. They follow it.

SACGHS Meeting Transcript
February 12, 2008

We have an example where we have already included a clinical and laboratory institute standard for microbiology cut points for antibiotics. It has become the standard of practice across the country. Everybody uses it because it is available to everyone and it works.

So we are trying to look at what are the needs that are necessary and use existing mechanisms and information to get there rather than spend six years doing a proposed and final rule on all of these different areas. Then you don't know what the outcome will be.

DR. FERREIRA-GONZALEZ: The first two recommendations, Reed, talk to some of the issues that were identified for the need of the genetic specialty.

DR. TUCKSON: So we can go ahead and start drilling into these recommendations and see where they take us. I guess the question that was confusing is, it gave me the sense that all of the problems in this space could, by some people's recommendation, be addressed by the magical creation of a genetic testing specialty. Then when you start going through the recommendations that come forward, there are things that are well beyond just a genetic testing specialty.

So we set it up as if there was this magic wand. If you don't agree with the magic wand, you are a bad committee. What I think we want to make sure we do is to make sure we are saying the concern is [this.]

The solution to those that we recommend is [this.] I think we got a false dichotomy.

But with that as an editorial comment, let's zip through these and see what we are saying.

DR. FERREIRA-GONZALEZ: Do you want us to put in text something like that specifically?

DR. TUCKSON: Eventually I think we will have to come back and try to put an organizing framework that says the problem that this recommendation is addressing is, boom. The solutions are, boom.

DR. FITZGERALD: To that end, again, if you go back to that oversight map and the gaps that were identified on that oversight map, you can look right off the top. I think they have them down under Gap 3, or Gaps 9, 10, and 11. There is already some organization to that that will be wherever this is going to be.

DR. FERREIRA-GONZALEZ: So it is not just in a single recommendation that we addressed the particular issues that speak to what others are calling for the specialty to solve some of the gaps.

DR. TUCKSON: Again, we are doing a challenge, and again, it is fine. We are working backwards. It is contextual. We have been taking this big mosaic and taking it in pieces: piece, piece, piece. This piece is what, is what I'm trying to [understand.] How did we define this piece.

DR. FERREIRA-GONZALEZ: If we go, I guess, to the Genetic Testing Oversight Map, these recommendations in Chapter 4, Recommendations 1 and 2, will deal with the G3, G9 to 11, and let me get my list.

DR. TUCKSON: So the notion is how do you describe what is common about G3 and G9 through 11? In other words, what is our bag here?

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: No. 3 is inadequate CLIA requirements for proficiency testing. No. 9, insufficient resources, funding, and means to develop PT for all genetic tests. No. 10, no data exist on the effectiveness of PT versus alternative assessments. No. 11, PT based on test methodologies such as sequencing have not been developed in the United States.

DR. TUCKSON: So this is a bag almost exclusively around proficiency testing. That is what we are talking about.

DR. FERREIRA-GONZALEZ: Recommendation 1 deals with a piece of proficiency testing. As we move forward to the other recommendations we are going to deal with other pieces that were of concern to people asking for the CLIA specialty.

DR. TUCKSON: So let's go ahead and see what the solutions are fixing the proficiency testing problem.

DR. FERREIRA-GONZALEZ: So again, you have the green there. We have revised Part A of this recommendation to call for CMS to require proficiency testing for all high complexity tests for which PT products are available. In No. 2, we have also added "in order to promote the development of new PT products and facilitate performance assessment efforts" to the language of that particular recommendation.

DR. TUCKSON: That would be everything.

DR. FERREIRA-GONZALEZ: Everything. It just goes beyond.

DR. TUCKSON: If you have any high complexity test for which proficiency test products are available.

DR. FERREIRA-GONZALEZ: Yes.

DR. TUCKSON: If they aren't available, you must use an alternative assessment methodology, as is already required.

DR. FERREIRA-GONZALEZ: Yes. It is already in CLIA. Alternative assessments.

DR. TUCKSON: So the only thing that is not in CLIA now is if you have a high complexity test for which it is available. If it is not available, there is something to do.

DR. FERREIRA-GONZALEZ: Yes.

DR. TUCKSON: So if you have a PT available, you currently get a ride. We are now saying no more rides.

MS. ASPINALL: Just for a limited number right now.

DR. TUCKSON: Right now the operative word is "high complexity." We will come back to that. All high complexity tests, as a result of this, now must have proficiency testing.

DR. FERREIRA-GONZALEZ: The way CLIA is now, it is explicit about PT for 83 specific analytes, or regulated analytes. What we are doing is taking out the 83 specific analytes to talk about every high complexity test.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: And the 83 stay in.

DR. FERREIRA-GONZALEZ: No, we will take the 83 out.

MS. ASPINALL: Basically, 83 is not a filter anymore. Is that what you are saying? The 83 analytes was a filter that kept people out. We are taking that filter off. More tests are going into the funnel.

DR. TUCKSON: So more tests are going into the funnel. But at the end of the day, no high complexity tests now will go unregulated. We have closed the door. Nobody slides.

DR. FERREIRA-GONZALEZ: For PT purposes.

DR. TUCKSON: For PT purposes.

DR. FERREIRA-GONZALEZ: For PT purposes, if you are doing high complexity testing, you must do PT if it is available. If not, you have to do alternative assessment. Mara.

MS. ASPINALL: I don't want to get back into the other discussion, but theoretically, if there is a DTC test that is not considered health that is high complexity, and I can't mention one.

DR. FERREIRA-GONZALEZ: We will deal with that. We need to bring them back in.

DR. TUCKSON: We will do that with the definition. Good for you, Mara.

Now, let's just go back through the basics again. Just for the average person to get how we write our language, what does the proficiency testing on this guarantee? And what doesn't it guarantee?

DR. FERREIRA-GONZALEZ: Well, the proficiency testing will assure that the laboratories that are performing specific testing, either FDA, CLIA, or laboratory-developed tests, will actually have a process to check that they are putting appropriate results, or the correct results. So it speaks to the analytical validity of the test.

DR. TUCKSON: Now, the high complexity bar; is there something important that is not being stated that is lower complexity that slides under the radar, comes out, and bites me in the butt?

MS. YOST: I think in the long run the analysis has to really look at all testing that is being performed and determine how best to describe the tests that should be covered by proficiency testing.

Clearly, there are 2- or 3,000 different tests that a laboratory may perform. Not every laboratory does. The majority of labs in the country are very small and probably do a menu of 20 tests because they are doctors' offices and they do patient-related testing for that particular visit. But for the larger laboratories, they do have huge menus that constitute thousands of tests.

You want to use tests that are going to test the laboratory, challenge the laboratory, so that if you do one test on a machine that does 25 different tests simultaneously with the same method, you only have to do one of those for PT to get whether or not the lab is doing it correctly. You don't have to do all 25 of them.

SACGHS Meeting Transcript
February 12, 2008

So you have to come up with a way to craft that proficiency testing requirement to allow for challenging the laboratory to ensure the accuracy of its testing but not making them do it just because.

DR. TUCKSON: In your answer, Judy -- I need the Committee to make sure as we try to get this nailed -- it sounded like you said there was a ride for somebody that got a free pass.

MS. YOST: Right now there are 83 out of those 2- or 3,000 tests that are currently in the regulation. But anything else that the lab does, as Andrea indicated, the lab still has to do that alternative assessment twice a year.

DR. TUCKSON: You mentioned something about big folk and then little folk.

MS. YOST: We have different sizes of laboratories. We have 200,000 labs in the country, and probably 80 percent of them are very small: clinics and doctors' offices sort of stuff.

DR. FERREIRA-GONZALEZ: Those will be moderate complexity or low complexity?

MS. YOST: Right. But a lot of the tests that currently are under PT are moderate complexity right now. So we can't leave them out necessarily because they are used as diagnostic tools in laboratories.

DR. TUCKSON: Is it true, from what you have said, that even with this recommendation there will be some laboratories that are performing genetic tests that will not be covered under CLIA for proficiency testing?

MS. YOST: If a genetic test is not high complexity. Under this recommendation just on its face.

DR. TUCKSON: Therefore, just to make sure from the Committee's sense, why are we comfortable that non-high complexity tests don't need to be reviewed?

DR. FERREIRA-GONZALEZ: I think today we can say with some certainty that all genetic tests are high complexity tests.

MS. YOST: Right now. It depends on how you define it.

DR. TUCKSON: We seem to have some uncertainty.

LT COL McLEAN: I'm just very concrete. Could I have an example of a high complexity, medium complexity, and a low complexity test? Is PKU sequencing a high complexity test? I would say yes. So, what is low complexity?

DR. FERREIRA-GONZALEZ: There are certain people saying what is a low complexity genetic test.

MS. ASPINALL: I guess it goes back to the fundamental issue, which is definition of genetic. It is not inheritable, but maternal serum screening is probably not genetic. Most people think about it as low complexity.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: As we try to figure out the answer to Scott's question, let me ask CMS. Why would you be comfortable giving a pass to some category of test? Human beings get the test whether it is complex or non-complex. It is still my life.

MS. YOST: I didn't say I was. What I did say was that we need to look at the whole range of tests and determine what are tests that are appropriate for PT. If you want all high complexity, maybe that is one criteria, but then the second might be other types of medically useful types of tests that currently may not be listed there but are used in high volumes in laboratories as diagnostics.

DR. TUCKSON: Let's just take the posture that you would want the authority to evaluate tests for which PT are available and, for when they are not, alternative assessment.

MS. YOST: That is essentially what the plan is to do.

DR. TUCKSON: So we should take out the word "high complexity."

MS. YOST: Well, are there tests that the Committee would say we don't think should go through PT. We are going the other way. We are starting with the big pie and we are going to narrow it down so we can identify which tests are appropriate for proficiency testing since all non-waived tests are currently regulated in some fashion under CLIA.

DR. TUCKSON: Judy, I think I understand. I think I see where you are. Let me make sure. Outside of the field of genetic tests, are there tests that are provided to the American people that have not been tested? That are not under some degree of oversight? Is there any laboratory test that is given to Americans that are completely devoid of oversight? You can just do whatever the hell you want to do and put it out on the market.

MS. YOST: There are the waived tests under CLIA. The waived tests under CLIA basically only require that you follow the manufacturer's instructions. There are no other requirements for those.

DR. TUCKSON: What would that be?

DR. FERREIRA-GONZALEZ: The waived tests are FDA-cleared.

MS. YOST: All laboratories are regulated as long as they meet the definition under CLIA in some fashion. But it depends on the complexity of tests that they perform how stringent the requirements are.

DR. TUCKSON: I'm talking in this case tests, because that is the word we use. So there are tests that you waive. An example would be what?

DR. FERREIRA-GONZALEZ: But they are FDA-cleared. They are usually FDA-cleared tests that have been waived.

DR. GUTMAN: In order for a test to be waived, it first has to be either FDA-cleared or approved. So it has to meet the FDA evidentiary standard. However, whether you swear by it or add it, it is our standard. It then has to go through a second process.

DR. TUCKSON: So it wasn't just because you said "I don't care."

SACGHS Meeting Transcript
February 12, 2008

DR. GUTMAN: No, no. I can assure you that is not the case.

[Laughter.]

DR. TUCKSON: Let's keep this right on focus because we have to roll.

You have to speak English here. Are you saying that there are some tests that you are prepared to let this Committee go forward recommending that do not get an FDA waive pass and that you are not doing your number on? If you are saying that is okay, I want to know why. To me, this is pretty straightforward. This is a no-brainer. You take out the "high complexity" and you say "tests in the field of genetics." You don't do it anywhere else, so why do it here?

I just want to understand why. Are you making an economic problem, that you don't have the manpower to do it? Is it that people are lazy? What is it? Why not just do it? What am I missing?

DR. FOMOUS: Are you asking to take out "high complexity"?

DR. TUCKSON: Yes. Or tell me, why is it in there?

DR. FERREIRA-GONZALEZ: Reed, the waived testing, the manufacturer has to go through FDA clearance and then has to demonstrate specific criteria that is very hard to screw up with the test. Is that correct?

DR. GUTMAN: Yes. Waived testing wouldn't be a very good setting for proficiency testing because you are making the assumption that you are dealing with untrained users. We are looking for simple technologies that are highly well calibrated and highly well controlled.

But that begs the issue. That is waived. Let's take waived off the table. I think the question you are asking is moderate versus high complexity. Where I'm not so sure is whether you are mixing FDA-cleared versus lab-developed tests. Lab-developed tests theoretically shouldn't be on the market if it is operating outside of a high complexity lab, although I think there are loopholes and it is possible for moderate complexity.

DR. AMOS: What about the term "all non-waived genetic tests"? Is that appropriate?

DR. TUCKSON: Yes.

DR. AMOS: Does that cover it?

MS. ASPINALL: I think that is closer, but do we need the word "genetic"?

DR. AMOS: Yes, because that is part of the definition.

MS. ASPINALL: I think there is a tremendous debate.

DR. AMOS: That is what we are talking about here.

MS. ASPINALL: Sort of. But we talk here about high complexity tests, some of which are genetic, some of which are not. The definition of genetic, many tests are low complexity and

SACGHS Meeting Transcript
February 12, 2008

may be genetic. So I like "non-waived," but I don't think we need either "genetic" or "high complexity." If a test can have a PT, it should.

DR. FERREIRA-GONZALEZ: I think for the waived tests, the way it gets approved --

MS. ASPINALL: Non-waived.

DR. FERREIRA-GONZALEZ: Non-waived, non-waived. The idea we are wrestling with here is changing this recommendation to "CMS should require PT for all non-waived tests for which PT products are available."

MS. ASPINALL: Yes.

DR. TUCKSON: And, if it is not available, you have to go down Road B.

MS. ASPINALL: Yes.

DR. TUCKSON: I think what we are agreeing to here is nobody gets through scott-free. The FDA may decide to go through some rigorous rigmarole, which we will come back to later, that says you get waived. But they have been dealt with. Somebody has grabbed them by the neck, analyzed the hell out of them, and said, "Okay. You get waived."

Then you have everything else that is left. If you are not waived, you are going through PT if there is PT available. If there ain't no PT available, you are going to go down Route B. But nobody gets through just because.

Is that accurate? Have we missed anything?

DR. AMOS: Yes. Where does "research use only" testing come in, Steve?

DR. GUTMAN: Hopefully it doesn't have anything to do with anything anybody here is talking about.

DR. FERREIRA-GONZALEZ: Let's leave that out. Let's leave that out, please.

DR. TUCKSON: So we have closed the door on all these things. We will come back to getting specifically into what does it mean. I don't know how good Route B is.

DR. FERREIRA-GONZALEZ: As a further recommendation, we are asking for research. So the idea is we are going to change [the recommendation to] "CMS should require PT for all non-waived tests for which PT products are available." So, "In order to promote the development of new PT products and facilitate performance -- efforts, HHS should fund studies on the effectiveness of other types of performance." That really goes to your point, Reed.

I think it has been proven that alternative assessment works, but we don't have the data. So we are asking them to fund some studies and also to look at other ways to do PT and more of a technology and methodology based like they do in Europe. There you have PT that is based on sequencing and you send your specimens. You have to sequence and get the right sequence, and then anything that actually is in your laboratory sequence space will be sufficient or covered for the PT testing.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: I would only modify it slightly. Instead of the word "determine whether," to say "to ensure that." You have to set out with your goals.

DR. FERREIRA-GONZALEZ: You need to keep in mind, too, if we look at genetic testing, some of this testing is for rare disorders. So we are not going to have vendors that are actually going to develop PT products. It is just not feasible economically. We have to have a route where we are assuring that the laboratory is still checking the analytical performance of the assay is working well.

DR. TUCKSON: I think this is good. Are we being mamby-pamby on this thing? Are we doing what we are supposed to do? Somebody said we are being [mamby-pamby.] Are we being too timid?

DR. FERREIRA-GONZALEZ: No. I don't think we are timid. I think we are really very aggressive.

DR. TUCKSON: Are we killing innovation?

DR. FERREIRA-GONZALEZ: No. Again, Reed, I think what is very important here is that if there are no PT products available there is alternative assessment. So there are other ways to get to this. We are not hampering the innovation of the testing. If your first one brings in a test that you have shown clinical validity, you can develop alternative assessments and continue to offer the test, but we make sure that the laboratory is checking into the analytical.

DR. TUCKSON: So, when are we going to get to the FDA part and the Route B part? The Route B part we are getting to now. We are not just saying that just as some little jive thing but that is going to be real. That is what that says, right? That Route B is real.

DR. FERREIRA-GONZALEZ: Yes, it is real. We are currently doing it.

DR. TUCKSON: Then we are going to eventually come to the resources for the CMS to be able to do it, which we will come to in a minute, too, right? Okay.

DR. STRAUBE: On your previous slide, the third sentence. Immediately following it, it says "In principle, genetic tests and/or other high complexity tests should be required to undergo PT." That probably should be changed in light of the change we just made in No. 1.

DR. FERREIRA-GONZALEZ: We change things here and there and then they get out of sync. So tonight that is what we are going to be doing, reading this. Everybody has homework for tonight, to read this.

DR. TUCKSON: I see what you are getting at with the studies of the effectiveness and we are going to make. There is an implied aspiration here which I would like to make more explicit. They should be as robust and therefore you want to study to make sure that they get to that level of robustness. It is just a little weak.

So, think about it. It could be the alternative assessment is as robust, is what I'm being told.

DR. FERREIRA-GONZALEZ: Yes, Mara.

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: Just a suggestion in terms of timing. Maybe getting through it all and that going back. Because we have to go back in terms of timing and putting things on the map.

DR. TUCKSON: Just keep that in your mind, folks.

DR. FERREIRA-GONZALEZ: But we also have to have in mind that actually there are different volumes of different tests. So there have to be other forms of evaluation.

DR. TUCKSON: I understand.

DR. FERREIRA-GONZALEZ: So let's go to Part B, that will deal with some of the issues specific to specialty and CMS. CMS should consult or contract with experts in the field to train inspectors of genetic testing laboratories. Training by such experts will enhance the inspectors' understanding of the technologies, processes, and procedures utilized by genetic testing laboratories and equip them to assess compliance with CLIA requirements. In addition, CMS should identify and evaluate innovative alternative mechanisms to inspect genetic testing laboratories.

So this gets to the point that CMS had already put in place and where they are going to hire more inspectors and actually train them to do that.

DR. TUCKSON: The College of American Pathology says everything is fine now. We are saying go further.

DR. FERREIRA-GONZALEZ: No, we are saying continue to implement. We are behind CMS in the implementation of these specific changes to the process of educating the inspectors and getting more inspectors. But even though they have already undergone the process of doing this, we want to make sure it is in the recommendation to assure that it really moves forward. It is just a reaffirmation of what they are doing.

No. C is, as recommended in the 2006 Government Accountability Office Report on Clinical Laboratory Quality, CMS should use revenues generated by the CLIA program to hire sufficient staff to fulfill CLIA's statutory responsibilities, and the program should be exempted from any hiring constraints imposed by other agencies.

DR. TUCKSON: So let's go to No. B. The question is, what is the standard. I'm trying to push here. What No. B doesn't say, or does it say, the bar right now for inspection we are okay with. Are we actually okay with the bar now? Are we saying that the current inspecting process is A-okay?

DR. FERREIRA-GONZALEZ: No. What we are saying here is that the inspectors require additional training to deal with genetic testing laboratories.

DR. TUCKSON: So we are saying they need more training. The bar should go up. And that, they should also identify and evaluate innovative alternative mechanisms to inspect genetic testing laboratories that meet a higher standard.

DR. FERREIRA-GONZALEZ: No, that is not a higher standard. Today there is no training of the inspectors to inspect genetic testing laboratories. Mara.

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: To be fair, it is a strange analogy but sort of a CME idea. It is working reasonably now, but we want to make sure that those who are in this field are up to date with new and evolving science. I think about it as CME. Let's make sure that these folks are continuously trained and up to date without fundamentally changing the whole system.

DR. TUCKSON: I'm really appreciative for that articulation because that is what I want to make sure that I understand that I'm signing on to. Are we signing onto basically saying that the CME, the status quo today, is pretty okay, that we are okay with that, we just want more of it, or are we saying it needs to go up a notch and that if you are going to find alternative mechanisms you want things that are at least as good, if not better than today.

But the bottom line is, are you okay today. I'm trying to understand whether or not our public comments in any way challenge that assumption that it is okay today. I'm not sure I know what they are saying.

DR. FERREIRA-GONZALEZ: I think there are concerns about the lack of knowledge of some of the inspectors about genetic testing. This will solve some of the issues. We will have a work force in CMS that will be knowledgeable how to inspect the genetic testing laboratories. But there is the same bar. We are just adding more education to the current inspection process.

MS. YOST: Let me please speak in defense of them, please. These are all experienced laboratorians with multiple years of laboratory experience before they become inspectors. We teach them about the regulations. We teach them how to interpret the regulations, what to look for in the laboratory to ensure that the laboratory is meeting the regulations. We teach them how to interview. We teach them how to go through the laboratory and observe testing and gather information, analyze that information to determine whether the laboratory is in compliance.

We teach them on a very broad-based level so they can go into a toxicology laboratory, into a cytology laboratory, into a histology laboratory and be able to identify does that laboratory have qualified people.

DR. TUCKSON: I've got you, Judy.

MS. YOST: This is very specific knowledge that we are asked to share, and we have already done it. We have started that process.

DR. TUCKSON: So look, you are doing fine work. You are working your butts off.

MS. YOST: Yes, we are.

DR. TUCKSON: I appreciate that. You are saying what you need to say. I'm going to let it go from this, and I'm not on a soapbox. I'm trying to get absolute clarity here. A very proud government official should be proud of her agency and her people. Have we heard significant testimony in front of this Committee that says the status quo, even though it is terrific, needs to be better? All I'm asking is, have we heard people say it has to get better than it is today. If so, are we dealing with it?

Now, I'm seeing people shake their heads that say that our testimony from external people is that we don't have any critical people screaming mad about today. They just want more of it and so forth. Is that what we are hearing?

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: Yes.

DR. TUCKSON: You all have read all that, every little detail?

MS. YOST: I have a little summary of the comments and looking for A, B, and C. Very few people commented on it. The few that did were either positive or neutral, and there are very few that were very negative --

DR. TUCKSON: Therefore, we are going to do some things to make it better. We are going to add more training. We are going to do all the wonderful things that Judy has said. Let's move on. Nobody seems troubled.

DR. FERREIRA-GONZALEZ: We are adding here that CMS should be exempt from the hiring freeze to make sure there are enough inspectors and resources.

DR. TUCKSON: Now, do they have enough resources today?

DR. FERREIRA-GONZALEZ: No.

DR. TUCKSON: No. So, where is our recommendation to add more?

DR. FERREIRA-GONZALEZ: No. C. We are telling them to use the revenues from the CLIA program.

DR. TUCKSON: Why aren't they doing it now?

DR. FERREIRA-GONZALEZ: Because there is a hiring freeze.

MS. YOST: We actually did get exempted from the hiring freeze. Because we are user-fee funded, we have been removed from the normal CMS [hiring freeze.]

DR. TUCKSON: Done. Anybody have any other comments about this?

[No response.]

DR. TUCKSON: Done. Move. Next. Next, next.

DR. FERREIRA-GONZALEZ: Recommendation No. 2 requests that funding be assured for the development of reference materials, methods, and samples for assay validation, quality control, and performance assessment along with other steps to address gaps in analytical and clinical validity data.

We did not revise Part A or B of this recommendation. We revised Part C to include that an initiative for enhancing public reference databases should encourage robust participation and need to consider mechanisms for anonymous reporting and protection from liability for encouraging information sharing.

Do we have any questions about this recommendation?

DR. AMOS: Andrea?

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: Yes, Mike.

DR. AMOS: Do we want to stick on this one first and then go back? I have a specific comment on No. A.

DR. FERREIRA-GONZALEZ: Okay. Go back to No. A.

DR. AMOS: One of the things that needs to be clear is that there are really two types of standards. There are standards for the analyte for a specific test, but there are also platform standards for microarrays or mass spec. Those are being developed.

So what I recommend is that we change the wording after the last line, where it says "for assay." Following "assay," it should say, "for assay analyte and platform validation, quality control, performance assessment, and standardization," to emphasize the point there are two different types of standards.

So it should be "assay analyte and platform validation, quality control, performance assessment, and standardization."

DR. FERREIRA-GONZALEZ: Your next comment? Did you say you had another comment, Mike?

DR. AMOS: That was it.

DR. FERREIRA-GONZALEZ: Any other comments?

[No response.]

DR. FERREIRA-GONZALEZ: The next one, Part D, I just wonder. It says, "HHS should support the development and dissemination by professional organizations of additional standards and guidance for applying genetic tests in clinical practice." The intention of this Part D of the recommendation was to encourage professional organizations to also develop professional guidance with respect to personnel training in interpreting genetic testing.

Maybe we can either add here in Recommendation 2-D, but maybe it has to go back to Recommendation 1, that CMS can draw from these professional organizations' recommendations to develop interpretative guidelines for the inspectors so they have a better understanding of who actually is appropriately trained to be directing different types of testing in this country.

MS. YOST: We would love to do that, but we would love to have all of your help to do that.

DR. FERREIRA-GONZALEZ: When you say all our help, what do you [mean]?

MS. YOST: We need your expertise.

DR. FERREIRA-GONZALEZ: That is why we are saying [we are] looking for professional societies to develop these kinds of professional guidelines.

MS. YOST: We will be happy to incorporate them.

DR. FERREIRA-GONZALEZ: Mara.

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: I think this is an absolutely critical recommendation because we know that, if you look at the adoption of tests, they happen only after professional societies recommend them.

What I would ask Judy or the Committee, can we be more specific as opposed to just what we have there at D, I think, that says we should support it? How can we be more specific and give that more teeth to make sure that it happens.

DR. FERREIRA-GONZALEZ: We have in Recommendation 2-D that HHS should support the development and dissemination of professional organizations of additional standards. So we are asking HHS to do that. But then what we need to ask is CMS to use these professional guidelines to develop interpretive guidelines for their inspectors.

MS. ASPINALL: I'm going back to the first sentence. What does "support" mean? How will they support? Is it money? Is it time? Is it access to data that comes about to be able to do it? Because many professional societies will say, "Good concept. We don't have the structure to do it. We don't have the samples to do it. We don't have the time or resources to do it." Can we be more specific to ensure that the connections are made?

DR. FERREIRA-GONZALEZ: Some of the problems that we have as a professional society is that we don't have enough resources to develop the process. So one of those could be support in money for the professional organizations. But I think working with the members of the different knowledge-generation agencies in coordination with the professional associations in development of these guidelines could be very important and have a major impact.

MS. ASPINALL: Joe just said provide the necessary support. I just want to get to a level of specificity that doesn't just say that HHS, with all good intentions, met with the societies and said, boy, we would really like you to do that. The societies are still stuck with the inability to get it done quickly.

DR. FERREIRA-GONZALEZ: There are two changes to these recommendations. One is that HHS should provide the necessary support for the development and dissemination of professional organizations of additional standards.

I guess we can do the change of the interpretive guidelines back in Recommendation 1. So we go back to No. 1-B. In No. 1-B we are talking about the inspection process and enhancing the training of the inspectors. Maybe we can put that particular here. We can say CMS should work with professional organizations to develop interpretive guidelines regarding personnel requirements for the interpretation of different genetic tests.

MS. ASPINALL: I was thinking that it mixed up No. B, which was, I thought, just focused on the inspectors and that it broadened it too much in terms of that. I guess I was thinking just deal with it in No. D, not change No. B, which I thought stood very well on its own.

DR. FERREIRA-GONZALEZ: I have it in either place. The idea is to tell CMS to use these standards to develop interpretive guidelines for their inspectors. So we can put it in No. D.

MS. ASPINALL: Although, I wonder. Maybe that is a way to put teeth into it. Either HHS or CMS, maybe if they have specific tests that they actually ask specific organizations to provide guidance within X period of time.

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: Yes, because I think that this gives CMS the means to go out to professional organizations and bring them in to work with the interpretive guidelines, not waiting for HHS to provide funds for this development. That is what I thought in No. B.

MS. ASPINALL: I think that is right. I just think No. B was the issue about training the inspectors. So I wouldn't put it in No. B.

DR. FERREIRA-GONZALEZ: You what?

MS. ASPINALL: I wouldn't put it in No. B. I would leave it in No. D.

DR. FERREIRA-GONZALEZ: But I think maybe we need to have a better understanding of what the interpretive guidelines are. Judy, interpretive guidelines gives more explanation to how you interpret the CLIA regulation for the inspectors to be used.

MS. YOST: This is a very narrow context. I think that probably it could go in either B or D, but in D it is much broader because, for CLIA purposes, you are really just looking at guidance to help both laboratories and surveyors be able to meet CLIA requirements or assess CLIA compliance and ensure quality testing as your bottom line.

So, wherever you think that fits better. I kind of assumed that in D. That is where I saw that. But this is a broader context because you are talking about applying the test in clinical practice. We are not going there for CLIA purposes.

DR. FERREIRA-GONZALEZ: That is C, clinical practice.

DR. TUCKSON: All right. D, that's it. Next.

MS. ASPINALL: So, can we put that same phrase in D? So B is all training inspectors and D is all professional organizations.

DR. FERREIRA-GONZALEZ: Yes. Again, the interpretive guidelines is to provide information to the inspectors.

MS. ASPINALL: I think it is more than just the inspectors and D allows it to be more than that.

DR. TUCKSON: So let's make sure. Mara, you have a good sense. Why don't you play with it, tweak it a little bit if you need to to try to tighten it up. This is not a major issue. Let's try to move on to the big ones.

DR. FOMOUS: So we are taking it out of B? Is that the final consensus?

[Pause.]

DR. FERREIRA-GONZALEZ: So, do we have any other edits for Recommendation 2? Any edits to Recommendation 2?

[No response.]

DR. FERREIRA-GONZALEZ: Can we move on to the next one?

SACGHS Meeting Transcript
February 12, 2008

DR. BILLINGS: Go back. Go back to C. "For example, and may a need to consider mechanisms"? Do you see what I'm saying? It is just an editing thing. "Such an issue should be structured."

DR. FOMOUS: What line is it on?

DR. BILLINGS: The last line in C. "Such an issue should be structured to encourage robust participation." I would question "robust participation." But, "for example, and may a need to consider."

DR. FOMOUS: "And may need." It is supposed to be "may be a need."

DR. BILLINGS: Whatever. I don't know what it is supposed to read. Whatever it is.

DR. TUCKSON: Fix it later. Let's go.

DR. FERREIRA-GONZALEZ: So we go back to Recommendation No. 3, supports a mandatory system of genetic test registration that uses CLIA registration data as a foundation. Wait, wait, wait.

DR. TUCKSON: "May," "maybe," we are not talking major policy here. We are just talking grammar. They will fix the grammar.

DR. FERREIRA-GONZALEZ: They will fix the grammar. Remember we are going to go back to this tomorrow.

DR. TUCKSON: It is 3:40. I want to get the big issues grappled with.

DR. FERREIRA-GONZALEZ: Do you want to have a break now?

DR. TUCKSON: No, no break. No. Oh, wait a minute. Wait a minute. Hold on. Time out.

I'm worried about the time. Ten minutes.

[Break.]

DR. TUCKSON: Let the record state that Judy Yost carried the flag marvelously for her team, despite repeated questioning on the part of the chairman. She held firm.

All right. We are going to press on. We are going to press on to the really hard stuff.

DR. FERREIRA-GONZALEZ: We are going to go to Recommendation 4 first and then come back to Recommendation 3. Just to keep it interesting.

Recommendation 4 asks HHS to convene relevant stakeholders to provide further input on FDA risk-based regulatory framework for laboratory-developed tests and consider models for assessing laboratory-developed tests that will not be subject to FDA review.

We revised Part A to expand the list of stakeholders and include laboratory-developed tests offered directly to consumers. We also added that the FDA risk basis should consider intended uses of laboratory-developed tests and likelihood of harms to patients or consumers if test results

SACGHS Meeting Transcript
February 12, 2008

are inaccurate, susceptible to misinterpretation, or if the test is misapplied or extended beyond the proposed intended use.

We also revised Part B to offer alternative assessment models for the infrequently performed laboratory-developed tests.

So, do you have any questions about this recommendation?

[No response.]

DR. FERREIRA-GONZALEZ: This is a recommendation that actually received a lot of comment, and we have different points of view from the different public [commenters.] Mainly the taskforce has different views on these issues. Furthermore, the public comment has provided different views of this particular recommendation, from everything regulated under FDA to actually leave it as it is in the current model, and some have it in between. Mara.

MS. ASPINALL: I know there will be much comment, but I will open it up with one issue on the addition. When it says "for infrequently performed LDTs," I don't think we should have the statement "such as those for rare diseases."

DR. FERREIRA-GONZALEZ: "Such as for rare diseases." We can put "rare diseases."

MS. ASPINALL: Excuse me?

DR. FERREIRA-GONZALEZ: We can put "rare diseases."

MS. ASPINALL: Well, no, I actually think "infrequently performed" is better than "rare diseases" because there are many rare diseases that are tested very, very frequently, whether that be PKU, whether that be cystic fibrosis or other things. Even though they are rare, the testing is very common.

But I think the issue is the infrequency of testing that is relevant, not the disease itself. So yes, I would delete that phrase.

DR. TUCKSON: Before we get into all the debates, can I just make sure that we all have the same background? Basically, why is it infeasible?

MS. ASPINALL: No, at least I was not getting to "infeasible." I think there is a different issue. I just wanted to say I think the purpose of that, and as I have talked to the Committee, it is about infrequently performed. The frequency of the disease itself is not relevant. It is about tests that are only done a dozen times a year.

DR. TUCKSON: I'm back at the fundamental Recommendation No. 4 preamble. The whole launching pad for this recommendation is that we agreed that applying the same regulatory framework to every genetic test is infeasible given the number of tests in use and in development and the cost and resources that will be needed to support such a structure.

So we are basically saying you can't do everything because it is infeasible practically to do it. Therefore, you have to make some tradeoffs. Also, by the way, if you tried to make everything fit, like the camel fits into the eye of the needle, you are going to delay patient access to important

SACGHS Meeting Transcript
February 12, 2008

new technologies and also delay an important step forward in defining the type of LDTs that would be subject to pre-market review, i.e. some won't be.

Now we are basically accepting that. We are saying, "Okay, public. You can't do everything, and we agree to that." So I want to make sure that we agree that it is infeasible, and it is okay that everything doesn't get FDA'd. Now the issue as you go forward is to decide what things it is okay not to have the highest level of scrutiny. Is that what this argument basically makes?

DR. FERREIRA-GONZALEZ: Yes. I have another comment, too, that has come to light as we go through the Genetic Testing Oversight Map that actually is now very, very clear. It has to do with some of the language that we have in the second sentence of the preamble, where SACGHS supports FDA regulation of LDTs and the flexible risk-based approach that agencies take to prioritize their review.

Now, if we go back to the Genetic Testing Oversight Map, you can see that for the laboratory-developed tests that will go through the FDA, laboratories will have to comply with FDA manufacturing control, FDA pre-approval inspection, and quality system regulation. At the same time, the laboratories also will have to go through inspection for CLIA, where some of the same issues will be again inspected by the laboratory.

So it seems that there is an overlap that is very onerous for the laboratories.

DR. TUCKSON: That is one of the things I think we are going to have to figure out a way to say. We need to be clear. Are we saying that there is an insufficiency of rigor problem or a gap problem or a duplicative problem? So there are three different things that can be going on here. I think we are going to have to be real disciplined about how we think through these.

On the one level, you could be saying you have two systems regulating the same thing. Sometimes you are saying that there is nobody regulating either one, FDA or CLIA. Then sometimes we are saying that we are making a judgment about the sufficiency of the review by FDA by sort of saying that not everything goes through the highest level of scrutiny and some things triage out.

When we start through this, let me make sure I understand. Of these recommendations that are coming in this section, are they speaking to all of those scenarios?

DR. FERREIRA-GONZALEZ: There is one speaking to this scenario for the testing that will go directly to the consumer without any CLIA oversight. We have a separate specific recommendation to deal with those particular tests. So that, take it out of this equation for now.

DR. TUCKSON: I think that one thing we want to be able to do in the preamble to these recommendations is to declare which bucket is the recommendation speaking to. When we look at this whole thing, is there any sense within the totality of these recommendations in No. 4, and again I come back to my one-note song here, that there are any free passes? Is there any hole where somebody gets to drive a truck untouched in this group?

DR. FERREIRA-GONZALEZ: Marc. Steve also had a [comment.]

DR. WILLIAMS: It seems to me that as we look at the subgroups after the preamble that we end up with a situation similar to the waived versus non-waived test. Here we have tests that FDA exerts pre-market review on and those that it chooses not to. We then recommend an alternative

SACGHS Meeting Transcript
February 12, 2008

pathway for those that FDA declines to apply pre-market. So there would be oversight for those tests that would avoid that pre-market review.

So the sense I have is we don't have a hole. They have to go A or B. There is no way to get around those two.

DR. TUCKSON: There may be a C where you get, somehow or another, FDA'd and CLIA'd.

DR. WILLIAMS: Right. Actually --

DR. FERREIRA-GONZALEZ: No, no, no. There is no C.

DR. WILLIAMS: Speaking to that, in A when we are talking about convening a group, I think one of the things we should articulate in that recommendation is that we specifically say "to avoid duplicative things." So that should be in A where we have this group coming together.

DR. FERREIRA-GONZALEZ: I will put it in the preamble. But I think Mara and Steve have comments to this.

MS. ASPINALL: Two things. One is I completely agree with Marc that there is no C, and a lot of the public comments say that. We can't have duplicative, overlapping, and non-consistent regulation. That would make C difficult.

But, you state that the FDA has taken the important step forward through the, I assume, IVDMIA with the pre-market review. Are we going to talk about whether we agree or disagree with that as a piece of the pre-market? Is pre-market review, in the way that has been articulated in the guidance, a good or bad idea?

DR. FERREIRA-GONZALEZ: There were a lot of discussions in our taskforce regarding how the risk base has been allocated for the IVDMIA. Part of the preamble is saying that that is why we have to bring the stakeholders together to further elaborate that particular concept of what constitutes risk base and how much weight we give to technology.

Is there anything specific you want to discuss about the IVDMIA?

MS. ASPINALL: I guess we have heard in the comment and discussion here everything from agreement to tweaks to fundamental rethinking of the pre-market review. So I think that we need to have a recommendation one way or another that says we agree with the guidance as stated today or we don't or we think that the philosophy of the guidance is correct but needs to be implemented over a period of years or a period of X. [Don't] just have it as a preamble because it is not clear to me whether that says we agree or disagree.

I would give you my opinion, but I wanted to start with the process issue.

MS. CARR: Can I ask for a clarification? When you say are we agreeing with the pre-market review laid out in the IVDMIA guidance, are you saying does the Committee agree with the nature of the review?

DR. TUCKSON: The sufficiency.

MS. CARR: Is it, or is it what they have chosen to subject to pre-market review?

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: The overall question is, do we require pre-market review of laboratory-developed tests.

MS. ASPINALL: To be fair, I have been involved in some of the discussion about this, but I think that for the clarification of the report itself, given this is one of the absolute key issues that is fundamental to it, we should clarify whether we answer your question, Andrea, either way. Do we agree that IVDMIAs or other LDTs should have pre-market review as stated. Should it be different.

DR. FERREIRA-GONZALEZ: There were discussions in the taskforce and the outcome or the majority view was that the tests that had a high risk should have some pre-market review through the FDA. Those are the tests that don't fall within this high risk according to the FDA. Moving forward in reviewing this, it will fall under this other public-private partnership that will actually do pre-market review.

So the recommendation says yes, there is a need for pre-market review.

MS. ASPINALL: But you are defining the pre-market review as a public-private partnership in a way that the FDA and the current guidance does not?

DR. FERREIRA-GONZALEZ: No, it is according to the risk. It will be one route or the other route.

DR. WILLIAMS: I don't know. The way I understand it, and maybe this is incorrect, but I think what we are saying is we agree that there needs to be a risk-based strategy. There was a lot of concern and a lot of discussion about how we interpreted FDA's assessment of the risk, and we thought that there needed to be input from other stakeholders to basically take more time around the risk issue to make sure that we are actually doing the risk stratification properly with the appropriate input.

So I see that as being appropriate and appropriately represented in the preamble and that basically A of the recommendation says this is a group we need to pull together to really look at getting input from to decide how to do the risk and how to decide which ones get pre-market and which ones don't.

So I think we are endorsing the concept but we have some concerns about the details of which that concept will be applied. This was our response from the public comments. These are the groups that say we think we need to have input. Of course, FDA has already received some input from some of these groups, also. So I think it reflects the ongoing process.

I don't know if Steve wants to comment.

DR. GUTMAN: I want to chime in, sure. A couple of things. First, even within the IVDMIA subgroup there are risks. It is not all Class 3, Class 2. There is actually being potential for Class 1 or Class 1-exempt products because we are not driven particularly by technology. Certainly the transparency issue is important to us, but it wasn't the technology per se. If you want to look at our webpage, we have approved expression arrays, microarrays, multiplex assays. We are not afraid of technology and its intended use.

So I would argue that even in the construct of IVDMIAs it can be parsed with some perhaps difference of opinion but some subtlety.

SACGHS Meeting Transcript
February 12, 2008

In terms of the issue that Andrea raised a couple of iterations ago, we are cognizant of the fact that there are QSR and CLIA differences. In that document, the IVDMA document, we do in fact commit ourselves to working with Judy to try and resolve any differences or build off of strengths or minimize redundancy.

I view that, actually, as a red herring. I actually think there are more similarities than differences and that the differences just need to be explained in a user-friendly way so that labs that are not only offering services but making products, because that is what I would characterize them as doing, might want to have design controls or caps or things that perhaps a regular lab might not want to have.

I think the most important thing to me, frankly, as a regulator -- but maybe not as a regulator, maybe as a patient, since I'm increasingly becoming a patient -- the most important thing to me is what Reed said, which is, is there A and what is the option to A? Is it a free pass; is it half price; is it three-quarters; is it a dime on the dollar?

Let me tell you what FDA's standard is, really quickly. You don't want to hear it because you have heard it before, but I'm going to tell it to you again. There is an investigational phase. So it comes in and it either has patient safety protections like these weird things called informed consent and IRBs. If it has risk to patients, [it has] these weird things like an actual submission to either the IRB or to the FDA. So it has investigational protections.

Before it can actually be commercially put on the mark and say "I am a legitimate lab test," it has pre-market review of discrete analytical performance, discrete clinical performance, and I would take umbrage with the term "plausibility," but I would argue it is correct to say we don't do evidence-based medicine in the way that Muin does. So we don't require that we demonstrate what the impact will be in 10 years on the healthcare system.

Then we have all kinds of interesting post-marketing controls. One is a requirement that they make product consistently and, if they don't, that they recall and notify players who were using the product.

And, we have MDR reporting. So when something goes wrong, you have to report it to FDA. Usually companies are anxious to work with FDA and fix what has gone wrong. Sometimes they are not so anxious. They are anxious to bury it under the rug, and we get into very colorful disputes with them and threaten action.

My first choice is, I tell them, that's fine. I'm going to put out a press release and let everyone know what is going on. Usually that works. Companies become very interested in cooperating.

That is the A. That is the A. It comes with research, it comes with pre-market, it comes with quality during the production, and it comes with post-market. That is the A.

Your job, or your job to give to HHS, is to figure out what the B is. I as a patient, not as a regulator, am fascinated with hoping that the B will at least be 50 cents on the dollar, not a dime on the dollar.

DR. FERREIRA-GONZALEZ: I'm confused.

MS. ASPINALL: I had you until the 50 cents versus 10 cents. I'm sorry.

SACGHS Meeting Transcript
February 12, 2008

DR. GUTMAN: You have to come up with something that is an alternative to what FDA does. It doesn't have the IDE. Or it can be just like FDA and you can simply create an FDA at your place. But it can be substantially equivalent to FDA and have the same functions, or it can be novelly different from FDA.

I forgot the most important thing because it is my personal passion, which is our obsession with labeling the truth. I can assure you our truth and the manufacturer's truth are not the same. Labeling the truth, and then putting the whole damn review in a place where every person can either swear at us or swear by us, but they can swear because it is in the public domain and it has been quality controlled.

Not to suggest any particular company lives on hype, but every company has the best and every company has pristine data and every company has the best claim. Of course that is business.

DR. TUCKSON: Steve, remind us again of which things in that scenario you just gave --

DR. GUTMAN: You have to choose. That is your job.

DR. TUCKSON: No, no.

DR. GUTMAN: I think they are all important.

DR. TUCKSON: You went to the wrong part of my question.

DR. GUTMAN: Sorry.

DR. TUCKSON: You jumped right when you should have jumped left.

DR. GUTMAN: You hit a nerve. I'm passionate.

DR. TUCKSON: Which things are outside of the FDA? That is what I don't understand.

DR. GUTMAN: Well, cost for sure. A letter with my name on it isn't a guarantee that the company will make a dime. They are often surprised or horrified or delighted. Reimbursement is outside. Actual use, as I think you said earlier. Practice standards, information, and articles will drive use. Off-label use.

DR. TUCKSON: I think you answered it, but let me make sure. In other words, you have the FDA process and then you said if there was another process. Why wouldn't everything be in the FDA process?

DR. GUTMAN: If you are going to have a registry, then the question I would ask is how do you know that the registry actually has correct information? Of course, what they are levelling at us, appropriately, is how will the FDA be nimble and quickly make changes to products. Well, the same question applies to the registry. How do you allow it to make quick changes and still make sure that those are legitimate changes?

DR. TUCKSON: I'm sorry, Steve. You are so good and smart. I'm not sure how we jumped to the registry train.

DR. GUTMAN: I thought that was B.

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: We asked a question before that.

DR. TUCKSON: You laid out a process for the FDA, Steve. Then we laid out a process perhaps as an alternative to the FDA. I'm just asking the very stupid question, why isn't everything in the FDA?

DR. GUTMAN: I'm asking the same question.

[Laughter.]

DR. WILLIAMS: I think it can be clarified very easily. The language in B says "for LDTs that will not be subject to FDA review." What Steve is saying is they are all subject to FDA review, therefore we don't need B. But that is not what we heard at our meeting.

DR. TUCKSON: Thank you, Marc.

MS. ASPINALL: Lots of people have said and discussed that things that are non-FDA today have been under CLIA and CMS, and we heard people say that regulation is sufficient. We heard other people say that regulation is not sufficient. I think that is very much the heart of the issue.

DR. TUCKSON: Which is exactly my opening question.

DR. GUTMAN: FDA does have to be careful what it wishes for.

DR. FERREIRA-GONZALEZ: I was going to say that, Steve, in light of some of the current reports on the infrastructure and the current ability to review these type of applications, what is realistic for the agency. That is what we are proposing these are the model to, to be able to offload some of these things.

DR. TUCKSON: Everybody is really, really precise now. First of all, at one level, our job is to be practical and not ridiculous. However, our job is also, as I understand it, to define the optimal state and then you work backward from there.

I would love for us to be able to make one statement in our Chapter 4 Recommendation 4, mother, God, and country table setting. The optimal situation would be that all ta-da gets whatever. You say this is what ought to occur. That is what we want.

However, after doing meticulous homework and so forth and so on, the FDA says ain't no way in hell you are ever going to get enough money to be able to actually do this in real life. For every test, the same thing.

We were impressed by that, although we are not scared to recommend what is important to the American people. But we also are practical people, and it seems there has to be some tiering, some hierarchization. But everything gets something, and the rules of hierarchization are the following.

I think that is what we are trying to say. I'm trying to see how our recommendations say that.

SACGHS Meeting Transcript
February 12, 2008

DR. AMOS: I actually think that we don't have enough information to make a recommendation on this just yet because we have not done a thorough economic assessment of the impact to markets, to innovation. The group that we have is not really qualified to do that.

DR. TUCKSON: Great point. Unfortunately, the null hypothesis doesn't exist for us.

[Laughter.]

DR. TUCKSON: We are in the position of having thought about it as best we can and making recommendations. So what you have said is that maybe what you are doing is tempering the degree of zeal or certainty and so forth, but at the end of the day, we can't avoid it. We have to make the choice. We have to make the call based on best input.

Back to this. Can we just simply define the optimal state?

DR. FERREIRA-GONZALEZ: I think we also have to keep in mind that we have the laboratory-developed tests and you also have the laboratory or the laboratorians that offer the test. It seems to me there are two sets of regulations, that some of them are overlapping and some are not, that could be overly burdensome to the laboratory. We can actually maybe stifle some of these innovations by over-regulating this system.

DR. TUCKSON: I understand. I guess what I'm asking the Committee and all of us is, look, we can get caught up in 8 million machinations of everybody's special interest and every reason why the FDA people are going to get pissed, the laboratorians are going to get pissed, Uncle Sue is going to get pissed.

At the end of the day, can't we just clean the slate and say we are not worried. At one level, you have to start with I'm not worried about everybody's special interests. I'm worried about the people. You have to say to the American people this is the optimal situation and then from there you work backward.

DR. FERREIRA-GONZALEZ: Muin.

DR. KHOURY: I think the end of your tenure, boss, here we are seeing the great side of you.

[Laughter.]

DR. KHOURY: So, what do we want. Let me put this public hat on. We want good tests that pass through a certain amount of standards that have analytic validity, good clinical validity. I think Steve just described the gold standard, so to speak, that FDA process. What he is challenging all of us is to design the Plan B where you get 50 cents for the dollar or 10 cents for the dollar. That is what we need to think about.

Now, people are selling stuff that is not validated out there, and you drive a train through the whole process here, from here down to the consumers, going around all of the railroad. You don't even have to go through CLIA, I think, if you go this way.

So, could we design, with Steve's help and with CMS's help, together? This Committee can make that recommendation, describe what the ideal is, which is truth in advertisement and minimum standards of clinical validity, analytic validity, quality control, clinical utility itself. That will depend on clinical trials, and maybe more creative ways of coverage with reimbursement can happen.

SACGHS Meeting Transcript
February 12, 2008

But you need a threshold below which stuff shouldn't be just going to the market. That threshold could be defined in the FDA process or some other process or a public-private partnership coming together, or stakeholders. But this is a group where I think we can make it happen.

DR. TUCKSON: By the way, Andrea, as you take it back over and keep driving us through, if it turns out that the best we can get, at least in terms of our statement, is to write down what Muin just said, the public deserves a threshold that you can't drive a truck through. The way you do that is you have to close this door and that door and that door.

That is what this Committee is saying. We may not be able to get to the level of specificity that you absolutely want, but then therefore here is what you have to do to get to that level of specificity. Even though it is not the optimal report, at least it is a pretty damn good report. But above all, let's clarify where those holes are and close the door.

DR. AMOS: Reed, I agree with everything Muin said, but there is another piece to it. We want people to continue to develop the new tests and new technology. You have to balance the regulatory zeal with the commercial realities.

DR. TUCKSON: By the way, just to put that issue to rest, I'm glad you did that. That is a sober analysis. I have enormous, as you can tell, private sector interest and sympathies myself. I believe in that.

Let me make sure, though. Does anybody believe on the private sector side that unless you get a free pass of no oversight, [there is no other] way you are going to be innovative? In other words, are there any innovationists in the room who also say, "I believe in innovation so strongly that I should never have to pass any scrutiny"? That doesn't exist, either.

DR. FERREIRA-GONZALEZ: It doesn't exist either because today we have CLIA.

DR. TUCKSON: So there is no innovationist, I believe, who will stand up in public and say "No one should ever look over my shoulder." I just want to make sure. That issue is off the table.

DR. WILLIAMS: Didn't we hear that this morning in public comments? From one of our public commenters I think we heard exactly that this morning.

DR. GUTMAN: That is what 23 and Me said.

DR. TUCKSON: So we had one. Other than one?

DR. FERREIRA-GONZALEZ: I don't think they called for no oversight. They claimed they don't fall within the current oversight.

DR. TUCKSON: Yes.

MS. ASPINALL: I heard them say that today they don't know where they fit in the system, but I thought she specifically said we welcome appropriate oversight.

DR. TUCKSON: They just said that the rules don't apply to them.

SACGHS Meeting Transcript
February 12, 2008

Anyway, the bottom line is I think it is really important that we get this sense of balance. But I think balance does not mean that the Committee needs to be scared into apoplexy that says that you stifle innovation the moment you say "oversight."

DR. AMOS: But your question was what is the optimal state. It has to consider the whole picture. It really has to consider both sides of the equation.

DR. TUCKSON: Got it. So, too much. Now let's move forward. Can we all acknowledge the general tone of Muin's comment that what we want to try to do and now what we are moving toward is from that sort of basic sense that there should be review. Now the question is, what is the nature of that review and by whom.

DR. FERREIRA-GONZALEZ: I think Steve has a [comment.]

DR. TEUTSCH: It follows from that. What I see in these recommendations is that minimum threshold is a risk-based threshold that should go through FDA. That is what we have come to as a Committee. Above some level, and we need a group to decide what that level is, it should go through FDA to protect people adequately, economics or no economics. Then we are talking about the things beneath that level that need to have another system which is going to be the one that oversees the LDTs.

I think we have that first level of review in here. That is my sense.

DR. TUCKSON: Let's define that first level of review.

DR. TEUTSCH: We are going to convene a group to figure out, given a certain level of risk of a test, above that level it should go to FDA review.

DR. TUCKSON: Now, let me just ask you. If FDA is doing it today, why do we need to restudy and why are we unsure of the adequacy of the review that they are doing today?

DR. FERREIRA-GONZALEZ: There have been some concerns.

DR. TEUTSCH: What we have is the IVDMA guidance, which we say it should not be based on the mechanism of the test, it should be based on the risk of the test.

DR. TUCKSON: Steve, you are not doing that today?

DR. GUTMAN: We are doing risk assessment. We are doing risk assessment in general for commercially distributed tests. The classification is actually a matter of public record. You can go in and look at our databases and see where virtually all the common tests, whether they are Class 1, Class 2, or Class 3. Most new tests will either be de novo Class 2 or Class 3.

So we are doing it, but we are doing it only for commercial tests, with the exception that IVDMA's we did say we thought that the --

DR. TUCKSON: So for the commercial test there is no risk stratification today.

DR. FERREIRA-GONZALEZ: Yes, there is.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: Then, why can't you just roll that over? So you know where I'm headed, and I think it is pretty obvious, this report calls for 18 commissions, 43 studies. The Secretary needs to allocate money to Bob, Joe, and Sue to study something or another. At the end of the day, what are you left with here?

I'm just trying to take out as much uncertainty as we can. If we are doing it today and if it is all right, then keep doing it.

DR. GUTMAN: Since we do have a risk-based program that we have been operating for 32 years now, it would be our preference not to scrap that and start with a new risk-based program. The program has been refined, and I'm not suggesting the program couldn't be refined further, but the idea of starting over again strikes me as novel but unnecessary.

[Laughter.]

DR. FERREIRA-GONZALEZ: Mara.

MS. ASPINALL: I won't disagree with the fact that it may be novel, but I think, Reed, in clarification to your question and then moving on, what we are talking about are LDTs. What we are talking about are laboratory-developed tests which are not commercially distributed in the same way as I think what Steve is talking about is. [These are] not IVDs and are typically looked at more as a service than a product in casual conversation.

I think it is very critical for us to recognize the differences with an LDT both in terms of time, effort, money to create it, the work that is behind it. Not the technology itself because I would agree that it cannot be technology-based. I also think we can't predict the technologies five years from now because they are changing.

But regulating a service is very different than regulating a product. The difference between CLIA and FDA, which goes back a few moments ago, is that CLIA, for the most part -- some may argue with this -- regulates the laboratory. Because there are a number of different LDTs going through that laboratory, FDA is regulating, on the other side, the tests themselves.

So that was the issue about fundamental overlap but not quite equal in terms of how this regulatory scheme is. I would say we need to recognize that a laboratory-developed test is not the same as a commercial kit with instructions and that by definition is made to be in everyone's hands and relatively simple to do going forward.

We need to, in the same way, have regulation that makes sense over all LDTs, and I would say not genetic versus not genetic, and at the same time recognizes the need for innovation because laboratory-developed tests have been the engine of many new tests. Many of these laboratory-developed ones start out, get to market relatively quickly, and then with the adoption and sometimes the innovation and lowering of cost, eventually become the commercialized tests that Steve was talking about.

I think it is absolutely essential that we maintain that system because that is the engine of many of these new tests and technologies, particularly in the field of personalized medicine becoming available to patients.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: As you said that, I recognize that there is a difference between the two. The issue then becomes is that difference so distinctive that it demands different assessment rigor. I appreciate not stifling the role small LDT plays.

The Genetic Alliance folk we asked this question of. I remember what Sherrie got to with this answer, which is making me think about this again.

So what we are recommending then is that somebody else figure out what is the optimal level of scrutiny for the laboratory tests? Even though there is a difference, Mara, I guess I'm still struggling with why would there be a difference in terms of its oversight?

MS. ASPINALL: I think that is the fundamental piece of the debate. I agree with you. I think we should take a stance and not say it is then yet another committee to do that.

DR. TUCKSON: There may be a difference without a distinction from an oversight point of view.

MS. ASPINALL: I would say there is a difference in the oversight, the need for oversight, the timing of oversight, and the access of information that is available to the lab doing it.

DR. TUCKSON: Steve, the process that you use now for the IVDMIAs, the things that you use now, describe that process so everybody has the same knowledge base.

DR. GUTMAN: Well, we have actually cleared only one IVDMIA. It went through a Class 2 de novo, so it was viewed as a moderate risk device. It had a prognostic claim, so that would have also made it a moderate risk device rather than a predictive claim.

We respected the fact that it was a very complex device. It had, I think, 70 or 72 different signals. So rather than do extensive analytical studies on each of the signals, we used the signature itself as the signal by which to determine performance characteristics. We did insist that the signal be reproducible and robust over time over operators so that we felt that if you got the signal you would always be getting the same signal.

We had no way to analytically credential this particular signal, so we credentialed it in the clinical outcomes that the company had reported and performed. So it was a very unusual submission. It shows, I think, the flexibility of our review process.

DR. TUCKSON: Did it cost the manufacturer a billion dollars to go through your process? Is that the thing that is going to kill off the poor lab people?

DR. GUTMAN: Well, no.

DR. TUCKSON: That is not the issue?

DR. GUTMAN: Again, I would argue that what would cost the companies the most money -- and Mara will know this and can agree or disagree -- is actually to do the studies that will demonstrate that they add value and will make my colleague from CMS happy, or somebody from BlueCross BlueShield happy. So I think those trials are the more expensive.

But I can't say it is a no-cost deal because we do ask annoying analytical questions about precision and repeatability.

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: I think it is important to realize that there are a number, for example, of academic medical laboratories that don't have the resources of the private sector that could think twice in developing this type of testing just because they will have to go through this process. We might be hampering some of that innovation because of this.

DR. TUCKSON: Muin.

DR. KHOURY: I just wanted to follow up on Steve's comment and your question, Reed, about does it cost a billion dollars to get to that point. While we don't want to stifle innovation, you [could] put something prematurely out there that could hurt people and things that might make sense or no.

Just going through the EGAPP recommendation that just came out in December, plus the EGAPP working group going through six or seven, many of them established, genetic tests, there is some missing information on both analytic and clinical validity. If you had to do it all over again, you would want to have that information while you are innovating because, at the end of the day, when you review things at the FDA level or in the EGAPP working group or the taskforce reviewing the data, the data has to be there.

So just the fact that there is no data, one can say there is no data. But if you rush it through the system, there will be premature release of technology.

DR. TUCKSON: You make a good point. The opposite of that point is a well-meaning nut in a laboratory who creates something that hurts people. I didn't have the money to figure out whether it would hurt anybody but I have terrific intentions, and therefore I released it. You wouldn't want to stop me, would you? Yes, we would. So there is a balance.

I guess where it winds up is -- and I'm just going to try this on you all and you tell me whether we can do better than this -- is the best that this recommendation can do is to take Muin's earlier comments about turning off all holes and that there should be a minimum threshold that everybody should get. That is the ideal state.

No. 2, we believe that the FDA model for reviewing whatever it is, is a good template that may not be able to be applied to all, but a high level of review by the FDA assures for the tests that meet the following criteria this is something that you really want to apply that rigidity to.

For things that don't reach that level of scrutiny but recognizing everybody has to go through something, we do call for some process in an urgent way that at least accomplishes a minimum threshold defined as [whatever.] That is what we are at least coming out of this thing with.

Now, maybe we can go further than that, and maybe our recommendations speak to how you lay that out. I'm putting a strawman up for you all to hit at.

DR. FERREIRA-GONZALEZ: I don't think that is very different from what we are recommending.

DR. TUCKSON: Let's go through the recommendation.

DR. FERREIRA-GONZALEZ: Muin.

SACGHS Meeting Transcript
February 12, 2008

DR. KHOURY: Given that you just said all of this, Reed, I think what would be important in that process is to put out the data that currently exist for the truth in advertisement. That is how we get back to this concept of the registry. Maybe we will revisit that point when we get there.

But basically, as part of this process, it is time to put the data out.

MS. ASPINALL: Muin, I think that that is exactly right. The devil then becomes in the details. The recommendation in concept, as Marc spoke about a while ago, that the FDA should exert some authority in this area but not do it in a way that stifles innovation is where the registry [comes in.]

And, I think it is fair to say the Committee moved from a voluntary registry to where the overwhelming public report was in terms of a mandatory registry. Some of the proposals, and I was involved in one, talk about having that for at least a period of time before there was any more formal FDA pre-market review just given the massive change that this is for the industry.

DR. FERREIRA-GONZALEZ: Are you recommending that in lieu of, for example, some of the moderate risk and lower going through review, just using the registry to convey that information?

MS. ASPINALL: Understanding Steve's comment about ensuring that the registry itself was accurate and up to date, which I think is an important issue, it has to be, the same way it is now, the burden of the companies or the universities or the laboratories to put that information up and, like today, the FDA can say "We have a problem with what you are saying." We talked about the FTC in terms of inappropriate advertising.

I think that that is a very important, at a minimum, relatively immediate -- like months to a year -- process. We can put up a registry, have full transparency with an industry, which I think is critical, and then from there evaluate where we go.

The other piece that I heard is some folks saying there are a dozen or two tests that would fit IVDMIA and a few hundred that would fit LDTs. I heard other people say no, there are a few hundred that are IVDMIA's and a few thousand that are LDTs. I can't say. My bias is there are probably more rather than less, but everyone has a very legitimate argument that says why their position is right.

So I am concerned today to put in a pre-market review, one, because it stifles innovation; two, I don't know what we are getting into in terms of the number of tests. So having an aggressive mandatory registry. This is Sarbanes-Oxley. The people who are putting it in need to sign off to say "I agree with this. It is truthful." I don't have a problem with that.

And, that we recommend a very prescribed registry for which every piece of information is the same so some company can't interpret it one way and another laboratory interpret it another way. Use that as the baseline. Put that in very quickly so that we have the full transparency and, with that, have the data to then potentially go on to have a more aggressive FDA process.

DR. FERREIRA-GONZALEZ: What you are saying, again, is that there is a different model, then. The first approach will be to have a mandatory registry for a narrow section of laboratory-developed tests, however we define this narrow section.

MS. ASPINALL: Well, narrow or not so narrow. Several of our folks said it should be broad.

SACGHS Meeting Transcript
February 12, 2008

DR. FERREIRA-GONZALEZ: High risk or whatever.

MS. ASPINALL: Or just all LDTs.

DR. FERREIRA-GONZALEZ: After a year or two of this, then we will have enough information on what we are actually talking about to be able to gauge the best route to go about doing the evaluation of the quality and the analytical validity and clinical validity of these tests as they go through the market.

MS. ASPINALL: Yes. To me, the beauty of the registry system and having that information available is that we can see it in our lifetime. It can happen relatively quickly. I heard a number of groups, and to be clear, I'm involved in some of them, that have said a registry is something that is doable. Not every group, but many of them have said, if you are going to have a registry, make it mandatory.

DR. TUCKSON: Mara, let me just make sure that we put this straight. The registry is a set of information that describes what? The status of its review? None of it. Just the analytical validity.

If you describe your ideal state, everybody gets something.

MS. ASPINALL: Yes, although I would say virtually everybody has something today. But under this system, everybody absolutely has something. But everyone has something today with a very few loopholes.

DR. FERREIRA-GONZALEZ: Now, let me make this clear. What you are recommending, then, is at this point that we do not make any assertion about the FDA role in the pre-market review but to create this registry with the specific data elements that allow us to get a handle on what the current testing is. From that, move forward to decide what model might fit with these laboratory-developed tests for pre-market review or not.

MS. ASPINALL: Right. What I heard Marc say earlier is the Committee talked about the principle of ensuring complete review and the principle of having the FDA involved I think is very important. But how to implement that, to me, is where innovation and practicality -- whether the FDA can do it over the right period of time and this actually gets enabled despite some legal issues, et cetera -- make this an alternative that allows us to move forward with something specific but doesn't cut off the FDA coming in at a point.

DR. TUCKSON: So here is what we are going to do. Let's go back through the recommendations and let's see what will change. I think that there is some tweaking needed on the preamble on Slide 4, Recommendation 4. The preamble stuff defines the mother, God, and country, but let's skip that for now. Go ahead.

DR. FERREIRA-GONZALEZ: Wait, wait, wait.

DR. TUCKSON: I don't want to wordsmith it, but it is something.

DR. FERREIRA-GONZALEZ: It is not a matter of wordsmithing. It is a concept. Maybe as they go through this registry there could be a role for FDA and CMS to work together to look at these types of things.

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: Many of the proposals say that. I think that is important.

DR. TUCKSON: Mara, describe, then, in your mind the relationship between the registry and the review. I don't think you mean the registry is a substitute for review. The registry is an assist to the review. It is also an assist for transparency. But the registry in and of itself does not protect you as citizens.

DR. FERREIRA-GONZALEZ: Well, it does protect.

DR. TUCKSON: How?

DR. FERREIRA-GONZALEZ: Because it starts forcing all the laboratories that develop laboratory-developed tests to start putting information out there.

DR. TUCKSON: Right. But the information has to be analyzed by someone.

DR. TEUTSCH: Someone has to vouch that the information is correct, on the analytic validity, and what we know about the clinical validity of these tests that warrant them being used at all. Right now we don't even have that.

DR. TUCKSON: That is essential for review. But you can't say to Mrs. Jones, average citizen, "Hey, Mrs. Jones, go to the registry. Look up the clinical validity. Now go have a conversation with your doctor." The patient is saying "I'm assuming this thing works."

DR. FERREIRA-GONZALEZ: Hold on. Let's say this. Analytical validity is covered under CLIA. So the problem is the clinical validity; is that correct?

DR. TEUTSCH: Exactly.

DR. FERREIRA-GONZALEZ: Now, we [can] put in the registry, where we have all this testing, all this information, but also we heard from Mike Watson today -- he just left, unfortunately -- about this database they are developing to start gathering this clinical validity information that can be even linked or built in together within this registry. Then we get to the piece of the clinical validity. If there is no sufficient clinical validity within this registry of the tests assessed through this database, then CMS or whoever can go back and say to the laboratory, "Your test here has no clinical validity."

DR. TUCKSON: So, who puts the pieces together?

DR. FERREIRA-GONZALEZ: Muin has a comment.

DR. KHOURY: Today many of the pieces are available. If as a consumer want to get this 23 and Me or whatever test, it is very hard for me as a consumer or provider to get all these pieces. I know I can get them if I work very hard at it.

These EGAPP reviews I come back to because there is quite a wealth of experience from these several reviews that are ongoing. Steve can attest to that.

It takes a long time to assemble the existing information on analytic validity and clinical validity of the tests, and these are sort of low-hanging fruits in the EGAPP market. So by requiring that formal registration in one place or in a virtual place, whether it is NIH, CDC, FDA, CMS, or

SACGHS Meeting Transcript
February 12, 2008

some kind of a virtual place, you can develop a registration process where people put in that information for people to evaluate.

Now, evaluators can evaluate it at any given point in time. The FDA process can kick in if they want it to kick in. An EGAPP-like process can kick in. It becomes, really, part of the data collection that will help the assessment of the validity of that information, but by requiring that form and then refining the data elements, we are helping the test developers say this is the kind of data we want, but also, we are helping them invest in the research that is needed to get that data. We are also helping the NIH and other funding bodies to do that research.

So this could be done under the auspices of the public-private partnerships if we want the buy-in from the private sector to steer the registry in a way that avoids mandatory but with strong steering from the private and professional organizations, et cetera. We can all work together to try to begin to populate this so that we can achieve, in the long run, that kind of idea that Steve has described.

DR. TUCKSON: That is the key thing. Again, the registry is information necessary for people to make the evaluations.

I want to make sure I understand the sense of the Committee. The Committee is not saying that it is okay, that the public is protected because there is a registry. Go look it up on the registry, Ms. Jones. Do the calculations, run the math, and you will decide whether you are fine. At some point, the registry is information that is used but there is some agency protecting the public that is saying it is okay.

That is all I'm trying to get to. Am I missing the sense of the Committee?

MS. ASPINALL: I don't know. My sense is it actually is a mix. To be fair, I think that many who have advocated for a registry -- and I won't say it again, but I have been involved in some of those efforts -- would say that it is probably best suited for virtually most of the tests that go through physicians. So it is not Mrs. Jones who goes to the registry, although she could. It would be a physician who goes to the registry, who would presumably understand the information that is listed under Test A, B, and C for the same condition.

So I think that this works best in those circumstances and that the level, I would imagine, of scientific rigor here is not necessarily based for a consumer. It is based for a physician so we have more complete information on analytical and clinical validity in that area.

I think the concept behind that is get it up and get it done because it doesn't exist now. So at an absolute minimum, when we talk about professional groups or other organizations, you just can't get that information now.

DR. TUCKSON: Steve has his hand up. One sense I get is, no one here is arguing against the necessity of a registry. That is important. I still want to try to make sure that we are getting to consensus that, okay, you have the registry. That is important. Let's fight for that. But, are we also saying you can stop there or are we saying you go further? Steve.

DR. GUTMAN: I have two points. First, don't underrate Mrs. Jones and her doctor, Dr. Smith, because her doctor may actually know less about the tests than Mrs. Jones in 2008. So the deal is there is a lot of ignorance among doctors about, in particular, lab tests. If you haven't read the

SACGHS Meeting Transcript
February 12, 2008

Rand Study in the New England Journal of Medicine in 2004, please read that because it is very sobering.

But that is the deal. You have crystallized it for me. FDA actually isn't opposed to, frankly, having moderate or moderately high or maybe high or certainly low risks put into a registry. In fact, that would be the only way we could survive.

What I was trying to say about the dime on the dollar is exactly what I think Reed is struggling with. I have seen too many bad data sets, either inadvertently bad or deliberately bad or something in between, where they pool data. It is too high in this one, it is too low in this one, and you pool them together and you have a statistical gold mine. I have seen matrix changes. It was under Judy Yost's authority, not mine. She said, "Can you send us the data?" and they said, "We will send you the 14 samples right away."

I'm telling you that that is what makes it credible. If the professional societies and the public-private partnerships step up and act in a pseudo-FDA way, then you can say to Mrs. Jones or to Dr. Smith this is a credible registry. It has been quality-controlled by an amalgam of the ACMG, AMP, CAP, AACC, ASM, maybe FDA or CMs. It is audited to make sure they know what they are doing and maybe make sure they didn't own stock in the ones that they evaluated.

But that is tricky. I'm not sure this Committee needs to resolve that, but I certainly hope in the recommendations that pass forward to HHS there is a desire for accountability in it and not just be registry, it be quality control of material entering that registry. I don't give a damn how it is done. I just would like, as a patient, to see it done.

DR. FERREIRA-GONZALEZ: But the quality control of the testing that comes in the registry is under CMS. The quality control is already checked by CLIA in the different reviews.

DR. GUTMAN: But CLIA samples. CLIA doesn't look at every single test. They come in and they will look at a lab with a dozen home brews and they will look at one or two and they sample in the middle of their review of personnel safety, quality assurance, the check on environmental. How can that possibly be?

DR. FERREIRA-GONZALEZ: Mara, then Scott.

LT COL McLEAN: I just want to point out that a really excellent registry is wonderful but it doesn't make it safe. The safety is still a wild card depending on what is happening with the clinical encounter. Just like a scalpel, if he is not a good surgeon you certainly can get cut.

MS. ASPINALL: I guess I like Steve's idea in terms of having a registry as a public-private partnership in some way with key organizations that are also putting their reputation on the line and saying that what is in this registry means something. I think having a registry like that, not immediately going to pre-market review but having a process that leverages the FDA time and CMS's time and has some key organizations that work together to do that. Again, one of the groups suggested something like that.

But I love Steve's idea to do that because that may, at least as we learn more about this industry, be able to fill the gap of getting the transparency and having all the tests together, which I think we all recognize is valuable. On the other hand, make it a registry with teeth that we know that if it is on that registry with a check mark that some group of professional organizations has gone through. It is very similar to the CAP inspection system.

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: Steve, tell me why this can't be again. This is the last time I'm going to ask this, and then I'm done with this thing. You have, in some definition, a high priority set of tests for which there must be pre-market review. FDA says, I have to review this thing. I'm going to turn to the registry. Look at all this terrific stuff in the registry. My job is so much easier now. I'm here to ascertain that about this test. Terrific.

Plan B is we make some decision that says because of some nature of the test it doesn't need FDA, it needs an alternative mechanism, but something is there for real oversight to review the test. They go, oh gee, look at this registry. It has lots of information in it. This makes our job so much easier. We will do what we do.

Third, Dear Doctor, if you are interested in knowing a lot more information beyond the fact that it has passed judgment, whatever that judgment is, and this is a legitimate test to unleash on the American people, go look at the registry. Oh my God, this is terrific. Look at all this interesting stuff.

I don't understand why the discussion keeps going do a registry and stop. FDA is off the hook. Everybody is off the hook. All you need to do is do a registry, return to your homes, everyone is safe.

[Laughter.]

DR. TUCKSON: I'm missing that leap. I just think if you have the registry, everybody else gets to do cost effective doing their job.

DR. GUTMAN: I'm a very transparent guy. I play poker by putting all my cards on the table. I think whoever gets stuck with this registry is getting a day job that is hard as hell because my job is a day job and a night job and it is hard as hell.

So if ACMG or AMP or AACC or COLA or whoever actually ends up quality-controlling the material and starting to discuss with the sponsor, "This precision study wasn't done right," wow, they have entertainment.

MR. DAYNARD: My problem is I haven't heard anyone assume the authority for reviewing LDTs and taking action against those who --

PARTICIPANT: FDA has it.

MR. DAYNARD: LDTs? I mean IVDs. I don't mean IVDMIA. I haven't heard anyone assume that authority.

DR. FERREIRA-GONZALEZ: If you have authority over MIA, they are LDTs.

MR. DAYNARD: I'm simply a mid-level official so I probably shouldn't say this, but the agency has a long history of being risk-based. So of course, the idea of looking at risk, you may argue what is high versus highest versus moderately high versus slightly moderate. You can argue about it, but the idea of a risk-based approach to regulation is inherent in the reg itself. Our Class 1 products are largely exempt and subject to QSRs. Our Class 3 products generally go to a formal and public panel.

SACGHS Meeting Transcript
February 12, 2008

I certainly don't want all of these tests because it is not possible. I do think the high risk tests belong in FDA.

DR. FERREIRA-GONZALEZ: Muin.

DR. KHOURY: The devil is in the details, obviously. But if the LDTs become part of the registry and this is mandated somehow and people start submitting data according to a specific format that is compatible with the IVD MIA, whatever we want to call it, there has to be some peer review process before it goes into the registry, or at least a check for initial glitches.

Now, people who are doing systematic reviews at the end to see whether or not the cumulative data makes sense, like EGAPP has been trying to do over the last five years, that could be done by an independent group or an FDA process if it is leaning that way. But I could envision a situation that requires a lot of thinking and a lot of groups coming together under this public-private partnership sort of umbrella.

But we cannot just take anything that people send to the registry as fact and then say to Mrs. Jones, "Go check the registry." It has to be peer reviewed. It has to have somehow gone through an initial validation process before we accept it as fact.

DR. FERREIRA-GONZALEZ: Like you say, the devil is in the details. If we are going to say that you have to put everything in the registry and everything has to be reviewed before we actually publish it in the registry, you will completely stifle everything. There has to be some kind of a process where we put stuff in the registry and there is a body of a public-private partnership that starts looking at this. It has to be funded and all these other details. But we have to be cautious when the devil is in the details.

DR. KHOURY: Right. There is some difference between NIH now requires for genome-wide association data or the sequences for the genome. Now everybody who is funded by NIH has to put their data in the NCBI DBGAP, which is the raw material from which people can do other studies.

The problem with genetic test development is you have a lot of data that is proprietary and you have competition between many, many groups. The way NIH did this with DBGAP was by saying everybody needs these data and these are pre-competitive type data. We need to know Gene X in relation to Disease Y.

So, could we construct a similar situation where instead of talking Test A from Company A and Test B for Company B, to develop an overarching data point on analytic validity and clinical validity of these classes of test by this group or that group or that group.

DR. FERREIRA-GONZALEZ: This is similar to what we heard from the College of Medical Genetics today. They actually developed a database where these data will be put together.

DR. TUCKSON: It is 5:05. We need to resolve this section before we leave for break. So as you all make your comments, let's start figuring out how we get to actual concreteness in the recommendations. We need to have people put on the table what they want.

MS. ASPINALL: I think I'm getting there. First comment: why don't we suggest the registry has a user fee, as many registries have, as the current IVD companies have. Either way, I think it will work out if we recommend a user fee-based registry, which takes away the issue of is there

SACGHS Meeting Transcript
February 12, 2008

enough funding to get this done, with a public-private partnership that approves things going into the registry with various organizations.

Maybe then the FDA has the ability to look at that registry and say we still have a question over what went into this registry. But the FDA, working with four or five professional organizations, has the ability to say these are the five things we want you to ask, these are the five things we need to check off. I'm not saying it is five.

Move forward in that way for a period of at least three years where we get the information, we get the transparency, we get it funded by companies with the lab tests, and we do a quality system so the registry itself, I completely agree, has to be respected as accurate.

DR. FERREIRA-GONZALEZ: Now, what you are saying that the FDA can go and start reviewing some of these tests, we are still saying that the FDA would have regulatory authority over laboratory-developed tests. That is the fundamental issue that we need to deal with for this recommendation. We can say that maybe the FDA doesn't have exactly the regulatory authority over LDT, but maybe it has to be kind of an interagency or so forth. That is the fundamental question we need to answer.

Now, we can say, then, after that that the FDA can review the high risk, or the FDA should for now hold off, let the registry develop, and as the registry develops, work from the registry because we will have built all these data elements and so forth. Work from the registry to actually exercise the authority over a number of these tests if they have questions about it. Marc.

DR. WILLIAMS: I am reluctant to even leave them here because I think we are so far out to sea I despair of ever getting back to shore. We have spent a lot of time talking about the registry, which I see as a means, not an end. I think that the fundamental question was very well stated by my colleague, whose name I can't read because it is tilted the wrong way. But, who has ownership of saying yea or nay?

This is a report on oversight. The issue that we have heard about is that we have had one test that has gone through an FDA clearance process. We know that there are hundreds, if not thousands of tests that are being used in the clinical arena today, which would seem to suggest that we have a pretty big hole that people are going through where, for a variety of reasons that are well articulated in the report, we have gaps in oversight.

Establishing a registry does nothing to deal with this. I think the critical issue here relates to the ownership of who in fact has the authority to say we look at this or we don't look at that.

As I have looked at Recommendation 4-A, the purpose that I saw of putting the consortium together is to try and see who is going to step up to the plate. Maybe that won't do it. Maybe that would just end up with more talk. But I don't see a registry doing that, either.

I think that ultimately, if we don't come down with some tangible recommendations to the Secretary that say somebody has to take ownership of this -- and maybe we can't define who it is but these are three suspects, get them in a room, and figure out who is going to do it -- it will be just another footnote on the lengthy trail towards reasonable oversight of genetic tests. I just think we are completely lost at the present time.

DR. FERREIRA-GONZALEZ: Any other comments?

SACGHS Meeting Transcript
February 12, 2008

MS. ASPINALL: In answer to the question Matthew raised, today CLIA owns oversight of LDTs? Would CLIA not say that?

DR. WILLIAMS: No, CLIA wouldn't say that. Or, they have said it, but in terms of actually realizing what they have said, it hasn't been done. That is the gap. That is the elephant in the room that we are not addressing.

MS. ASPINALL: You may go either way, but --

DR. WILLIAMS: That is what is in the report. Two hundred pages explaining exactly why we have this. The first rule in quality improvement is systems are perfectly designed to give you the result that you have. Our system is perfectly designed to give us the results of an essentially unregulated market for genetic tests.

MS. ASPINALL: What does CLIA regulate today if not LDTs? I guess that is the piece that I'm confused about.

DR. WILLIAMS: They are looking at the analytic validity of it.

DR. FERREIRA-GONZALEZ: But I think we also have to look at the reality. Like Reed said, what is their idea. What can we actually do to make sure we don't stifle innovation.

DR. WILLIAMS: Right. I am perfectly cognizant of that point. That is why I think the recommendations that we have come to to say let's at least get the players that we think are important in a room together and say, here is the problem you need to address. We need to have a tangible solution come out of the room.

We as a Committee certainly don't have any right answers that we can impose, but I think we can at least say here are the players that we think are important and we think that the Secretary should ask them to say what is the system that you would propose to fix this gap which currently exists.

DR. FERREIRA-GONZALEZ: So, do away with the current recommendation and say these are the issues that we have identified in the report, these are the three agencies that have some kind of overlap or not, they need to get together and figure out how or who is going to go about obtaining that.

DR. WILLIAMS: I wouldn't say it is getting away from the recommendations. I think that we have articulated that within the recommendations. I think it is in there. We can tweak it, but we have suddenly become focused on something that is in the recommendations but is only a part of the whole picture. If we just focus on that solely, we are going to lose what is really important, I think.

DR. FERREIRA-GONZALEZ: I think what we have focused on is very important to the entire recommendation, too, because the devil is also in the details of how we are actually going to do this.

DR. TUCKSON: Let's try to bring it on home.

DR. FERREIRA-GONZALEZ: Kevin, you have a comment?

SACGHS Meeting Transcript
February 12, 2008

DR. TUCKSON: No, no, no. I always defer to my colleague Kevin. It is never too late in the day.

DR. FITZGERALD: Sure. At the end.

[Laughter.]

DR. FITZGERALD: I agree very much with what Marc is saying here. Agreed, the registry is going to be key, but this other part is also key. When you started to say let's just total No. 3, I thought what we tried to do in 4-A was to make sure that in order not to stifle innovation, in order not to leave anybody out from around the table, everybody is supposed to be there. That is 4-A. When we have this discussion, we want to make sure those voices are there at the table so nobody later on can come back and say "You didn't listen to us. We weren't in on it."

DR. FERREIRA-GONZALEZ: But you are still assuming that FDA will be the body to regulate all these LDTs.

DR. FITZGERALD: I believe what we have here is HHS convenes these agencies. I don't think we claim necessarily in that 4-A, right?

DR. FERREIRA-GONZALEZ: In the preamble we do. That is the issue. In the preamble we do. Mara.

MS. ASPINALL: Kevin and Mark, I guess I have a question. I appreciate what you have said, but if we have a lot of different agencies listed, what worries me is that that will make it less likely that one would step up because it then becomes a very large committee and it takes a longer period of time to come to clarity with having a longer list of people rather than a shorter list of just CMS and FDA.

DR. WILLIAMS: It depends to some degree on the direction that they receive from the Secretary. If the Secretary says "Sit in a room and in a month I want an answer from you," they are going to do that. That is why I think we have to say this is really important. We can't create a solution as an advisory committee, but here are the people that can.

Again, whether it will be acted on, whether it will just again fade away, at least I think we can say we didn't pass the buck, and I feel like we are passing the buck.

DR. TUCKSON: Let's try to get to some consensus here and play this thing out. What we may have to do is have Marc, who has a good grasp of this, try to draft something.

So here's the deal. Let me try this and just see where we get. We say in our preamble something to the effect that, Dear Mr. Secretary, it is clear that there is a major gap in the oversight of genetic tests when it comes to the assignment and evaluation of clinical validity. That is a major, huge problem that has a truck that can drive through that hole all the way through to the end.

Therefore, we find that to be unacceptable. Our recommendation is that that reality is clearly identified and determined to be unacceptable. It needs to be fixed.

The solution to that involves a combination of approaches: risk-based assessment that goes through an FDA-like process that is used for blah, blah, blah, and potentially a separate process for less risky things that still meet the hurdle of protection of the public with legitimate oversight.

SACGHS Meeting Transcript
February 12, 2008

We define "risky" as attributes such as, and we have a few attributes in here as to what is high risk.

To accomplish this, we urge you to fix this urgently through a process of convening the appropriate agencies, blah, blah, blah, and in an expeditious way assign this accountability for this issue.

In making this recommendation, we are cognizant of the concern around innovation and not stifling it. We are also cognizant of the differential data requirements between different kinds of product manufacturers, the IVDTs and the LDTs and all that. However, with that cognizance in mind, we still cannot avoid the recommendation that every test has to pass some scrutiny.

Lastly, Mr. Secretary, a companion recommendation is, to facilitate this process there should be a registry. That registry needs to have the following attributes: blah, blah, blah. That registry will then make it much easier for the FDA review, the FDA-like review, and the alternative pathway review, as well as serve other public purposes.

MS. CARR: Reed, what is the "FDA-like"?

DR. TUCKSON: "FDA-like" is whatever that thing is that he is doing now.

[Laughter.]

DR. TUCKSON: She is challenging me because I was afraid to assign the FDA to be the grand poombah of this because you all made me nervous. I will be happy to have more courage. So I have more courage and say the FDA ought to be the thing. There it is.

DR. AMOS: I'm going to be a broken record. You have to have the evidence of harm to make such a strong statement. You have to have the data.

DR. TUCKSON: We have 10 minutes. I have thrown out a strawman recommendation. Now what I want to get are people who disagree, and be specific. They have already changed it. My weak, scaredy, fraidy "FDA-like" word has now been changed to "FDA." Now, what other modifications to this knucklehead proposal of mine do you want to make?

DR. FERREIRA-GONZALEZ: I think we have to write it down and come back tomorrow with it.

DR. KHOURY: Why don't you repeat what you just said?

[Laughter.]

MS. ASPINALL: I just have one clarification. I agree with the comments that say we shouldn't pass the buck. So what I was concerned about was that the first paragraph of 4-A was passing the buck back to HHS to make the decision.

MS. CARR: No, about risk. About the risk.

MS. ASPINALL: Just about the relative risk?

MS. CARR: Yes. FDA, bless its heart, did not get it completely right with its first attempt at regulating LDTs, which is the IVDMA guidance. That is what the preamble says.

SACGHS Meeting Transcript
February 12, 2008

So the taskforce is presenting this recommendation that we agree that FDA is the agency that has the authority and has the right mechanisms to review laboratory-developed tests to get at the clinical validity issue. But we also say that they didn't quite get it right the first time they did it, which is with the IVDMA guidance.

So 4-A says, convene a group of all the agencies and stakeholders to help FDA get it right. The reason they didn't get it right was because they, in our understanding, did not rely on what they say they always do, which is risk, but rather they relied on the technology. That is what we, the taskforce, found. So we want to provide some further input, although, as you said, FDA got a lot of input from the public on the guidance.

MS. ASPINALL: That helps me. I withdraw my comment because I was confused about having the multiple agencies. Now I understand.

DR. TUCKSON: What we are going to do is this. Poor Andrea and Reed and Sarah are going to redo this now, tonight, right now. Lucky Marc is off the hook with his one neuron dangling like a participle.

[Laughter.]

DR. TUCKSON: We are going to write this, and you will have it as soon as you walk in the door tomorrow. You will decide, hopefully, that it is close to what you want, you'll tweak it a little bit, but we are not going to fool around with it much because we have to move to the next issue.

Muin gets the last word.

DR. KHOURY: While you are doing Recommendation 4, take a look at Recommendation 3 because that [refers to] the registry. Maybe you can work on improvements simultaneously.

DR. TUCKSON: Thanks, Muin. I really appreciate that.

[Whereupon, at 5:28 p.m., the meeting was recessed to reconvene the following day at 8:30 a.m.]