SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

FOURTH MEETING

Friday, February 25, 2000
Polaris Ballroom
International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

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P R O C E E D I N G S (8:04 a.m.)

DR. McCABE: Good morning, everyone. Let's get started.

First of all, people have been asking me when are we going to finish up? We're scheduled to go till 5:30. Our deliberations are due to be done at 5:00. The last half hour is looking to the future. If we can come to absolute agreement in 20 or 30 minutes after the start of the discussion then we can be out of here a lot sooner, but my guess is that we'll be going till 5:30.

If people are going to leave early, maybe you could let Hope know that because I do need to keep an eye on the quorum. So at the break, if you could let Hope know when you're leaving, please let us know.

The other thing is that if you wish to move a little faster through Questions 4 and 5, we have to review what the public has said, and I want to go over that, but we really discussed some of these issues yesterday. Then we can move on to the deliberations sooner, but that will be sort of up to everybody and the discussion.

I think we really began the deliberations yesterday, even though we've been talking about the public comment, and I think certain things are beginning to fall into place or at least certain possibilities are arising.

So I think it's definitely doable. Again, we will have the skeleton of this draft document before we leave here today.

So now let's have Susanne and Alan give us a summary of the public comments on Issue 4.

DR. STOCKDALE: Good morning. Okay, Issue 4. What are the options for oversight of genetic tests and the advantages and disadvantages of each option?

The three most popular responses to that were consortium approach, federal oversight of some type or strengthening CLIA and CAP regulations, and those responses were about equal. There wasn't any one that was really favored strongly over another.

I'm not going to go through the advantages and disadvantages people listed. There's a sort of list of that on page 4 of the Web site analysis, but a lot of those were kind of obvious, like sort of things that people would say, I think.

For 4.1, information about the accuracy, validity, and usefulness of genetic tests is being gathered through research studies. At what point should an experimental task be considered ready for general use? Is it important for a test to be immediately available, even if its validity has not been fully established? Might the point at which the test is considered ready for general use be different for different types of tests? Since data on the validity of tests for rare diseases are especially difficult to collect, should special considerations be given to rare disease testing to ensure access to these tests, and, if so, what should the considerations be?

Most people were in favor of clinical validity and utility should be demonstrated before a test is introduced into clinical practice. There were another group that were in favor of variable criteria,

depending on the use to which the test was being put. People were in favor of genetic tests for rare diseases should be given special considerations.

About a fourth of the respondents thought that tests should be made available even if validity had not been established, although they thought that under those circumstances, the individual taking the test should be fully informed of the limitations.

Some of those people, I think, responding to that, the issues were that patient autonomy was part of the issue, and I think another part of the issue that came out there, certainly in the Web analysis, was people looking for a diagnosis, like parents of children, who have gone through diagnostic issues.

Issue 4.2. What level of confidence should individuals have, or might want to have, in the information they receive about a genetic test? Would the level of confidence change depending on the type of disease or the type of testing being done?

A high level of confidence in accuracy was the response to that one that was most popular.

4.3. Is making information available to the consumer about a genetic test, such as information about its accuracy, predictive power, and available therapy, a sufficient form of oversight?

There was strong support for necessary, but not sufficient, and a lot of people noted that the main caveat to that was that it was a really strong need to address the patient and consumer understanding of the information associated with the test.

Issue 4.4. Would one form of oversight be to review or inspect promotional material directed to consumers and health care providers to make sure that claims made are accurate? Is this sufficient oversight?

Again, people thought this was important, but not sufficient, need for oversight in other areas, and I'm going to, in the next couple of questions, I'm going to slipstream in some of the responses to questions in Issue 6, because I think they're relevant here.

In 6.4, which was on should tests be directly available from laboratories, the response to that was no, people should not be able to order tests directly from labs, again because of the need for counseling, and test interpretation was the issue.

Issue 4.5. Should genetic education and counseling provided by an individual, be provided by an individual, with special training always be available when genetic tests are offered? Should this apply for every genetic test or only some kinds of genetic tests?

People were generally in favor of that, either for all tests or for some tests, particularly predisposition, presymptomatic, and prenatal tests, and then again there was another issue as part of -- the question is part of Issue 6, 6.3, which dealt with whether health providers should require written consent, and whether lab assurance of consent was necessary.

People were generally in favor of informed consent should be required. There was less support for the lab assurances of informed consent. People thought that the need for written consent probably varied,

depending on the type of tests, and it may not be necessary for some tests, such as diagnostic tests. Again, an issue was the necessity of counseling again.

There were a few people that commented that they thought that the need for counseling and informed consent for all tests may vary over time as the public became more familiar with genetic testing, that that might decrease as a necessity.

Issue 4.6. Certain trade-offs may be necessary in order to ensure that genetic tests are safe and effective. Are consumers willing to pay for the cost of additional oversight of genetic tests? Are consumers willing to wait for the effectiveness of genetic tests to be demonstrated before having access to new genetic tests?

They were both willing to both pay and wait for additional oversight of genetic tests, but there was less consensus in the responses on the waiting question, which I think if you go back to Issue 4.1, there were a few people there, about a fourth of the responses there, where people thought tests should be made available. So I think that's probably not surprising that that reappeared again as -- there's a group of people that want tests to be made available immediately.

DR. McCABE: Thank you.

Susanne, do you have anything to add?

DR. HAGA: No comment.

DR. McCABE: Yes?

DR. LEWIS: One of the things that I'd just like to push on a little bit is when you said that people were not in favor of direct access to tests because of the need for counseling, one of the things you said yesterday is that a really good chunk of the people who responded to the Web site were counselors.

Can you tell me whether that response was sort of weighted by the fact that it was counselors reporting versus what people who weren't counselors, like the public --

DR. STOCKDALE: Well, I think in the responses I got on the Web site, that, yes, I think it's not surprising. The responses to the questions on the Web site, there was really strong support for counseling, more education, and I think that's not surprising given the large number of counselors that were responding there, and that the people who wanted direct access were parents, because there were quite a lot of parents responding to the Web site, too, who had gone through -- some of them recounted stories of diagnostic problems, they had a child with a disease -- they didn't know what it was.

There were a large bunch of people who had diseases that they thought should have been covered by newborn screening. So they were, you know, very much in favor of testing being available early.

DR. LEWIS: So the issue then would be people who had a sense of what the test would mean wanted direct access without having to go back to a counselor?

DR. STOCKDALE: Yes.

DR. McCABE: Other discussion of this issue? Especially I'd like to hear some discussion of the three options under 4, the consortium, the federal oversight, the strengthening of CLIA/CAP.

Yes, Joann?

DR. BOUGHMAN: As a result of going back through the public comments again last night, I'd like to just point out three or four that were repeated and, I think, important themes to be possibly captured here.

One had to do with in fact development of a consortium, but rather than just talking about oversight, repeating the point I made yesterday, there were several comments about the development of standards of care, standards of practice, or best practices.

Another one that in fact reaffirmed that current oversight mechanisms, if they are merely modified and enhanced and connected together, could be much more effective than the creation of entirely new entities. In other words, challenging us to be effective in building upon what is already available.

There were two or three clear references to the U.S. Preventive Services Task Force and the model created there, and I'm not familiar enough with that to know. I think that is a consortium model, if I'm not incorrect, but I'm not sure about that.

And there were at least two or three comments and a couple of these from within the laboratory community, including the American Society of Clinical Pathologists, who said that CLIA and CAP have the structures for oversight in place, but in fact it is the qualifications of the inspectors that may need to be looked at very clearly in the context of genetic testing, so that assessments could be made on quality control issues directly regarding genetic testing issues and laboratory qualifications to perform those.

DR. McCABE: Thank you.

David, could you tell us about the U.S. Preventive Services Task Force? Because I also had a question about what that was.

DR. LANIER: Sure. This is a task force that was established in the mid-1980s as part of the Office of Disease Prevention and Health Promotion, and it's a group of people similar to this in that they are non-federal people, but it's basically generalist clinicians who are on this group, and they have a pretty enormous charge of reviewing every preventable condition that could happen to man, woman, or child, and what they do is to review the literature in favor of using a screening test, and they look at every possibility of screening, from testing to counseling, and about every six years come out with a volume that actually summarizes the information.

So I think the one thing that they don't do that would be similar to what we've been talking about is primary data collection. They really have not been involved in that at all.

It's also a group that doesn't contain any specialists on genetics, and I think what they've done is to make some recommendations that have really influenced the policy and practices, though, both from the extent of what clinicians do and also what insurers are likely to pay for. So when the task force comes out with a recommendation that says that there is very strong evidence in favor of one type of screening, it's likely that clinicians will do that, and it's also likely that insurers will pay for it.

So from that point of view, I think it's a nice model to think about. I'm not sure that this group could take on the task, however, of reviewing every genetic test that might come about, and, you know, when you look at the book, it's about 500 pages.

DR. LEWIS: Is that the Clinician's Guide?

DR. LANIER: Yes, Clinician's Guide. This comes out about every six years. One is due to come out within the next year or two, an updated version of that, and they have touched upon some screening issues, particularly newborn screening, but not so much of genetic testing.

So I think as a model, it's something that we could think about here, but I don't think this task force could take on the entire work that we are talking about here.

DR. McCABE: I think that the comments were more in terms of structure. They were considering a similarity of structure, not asking for the task force to take on the genetic issues.

DR. LANIER: Good. I would be in big trouble if we were asking them to do that.

DR. McCABE: And what about the methodologies that you used for selecting?

DR. LANIER: Well, if there's any criticism of the task force, it's that the group have been too conservative, too strict in their recommendations, because what they do is to have different levels of evidence, and so they actually rate the evidence, and the best evidence would be randomized controlled trials, showing the effectiveness and few risks involved with each one of the tests that are used. Then they come out with strong recommendations in favor of it or strong recommendations against using this screening test.

They justified this by saying that the primary target audience are people who are in the general population and who are currently asymptomatic, and so unless you have a test that is going to be very useful for which there is treatment available, and that it's not terribly expensive, we shouldn't be requiring or requesting that this be done on a regular basis.

So they have a way of looking at the data, occasionally using meta-analysis to combine several studies, but what they were looking for would be several controlled trials that show evidence of a positive effect of the screening and improvement in outcomes for patients.

They also select conditions that have a high burden of illness, so they're not likely to look for prevention of minor illnesses.

DR. McCABE: How large is this group?

DR. LANIER: It’s about, I think about 20 people that are on it, 15 to 20, and they're like this, liaisons from agencies, but the decisions are made by the people that are there, and these are all, as I said, generalist physicians.

DR. McCABE: Wylie?

DR. BURKE: Yes. I'd like to make a couple more comments about the U.S. Preventive Services Task Force because I think it is a very interesting model for us, and clearly, were we to follow that model, we would need to convene a group that had the appropriate expertise, obviously including genetics expertise, obviously including consumer input, as we've had discussion, too.

What I think is most important about the U.S. Preventive Services Task Force, speaking from the perspective of primary care for the moment, is that it has developed a methodology, a way of looking at the quality of evidence, that is really unassailable.

So I think it's very important to separate the methodology of figuring out what the evidence is and what it says from the recommendation, and it may well be that what we want is a panel that does the first part and not the second part.

In other words, we may provide the most important service if we tell people what we know and tell people what we don't know, using a standardized methodology that is very open and very clear and very well-described, and I think one that will not be argued with. So what this body would be doing is saying authoritatively this is what we know. This is where we are in knowledge of current genetic tests.

I actually recently had occasion to talk to Al Berg, who's the chair of the U.S. Preventive Services Task Force, about a methodologic issue that will be extremely important in a genetics group, and that is how you handle systematically and appropriately evidence that's below Level 1, and what the U.S. Preventive Services Task Force looks for is randomized controlled trial data or well-designed case-control data to support their recommendations.

What we're going to have in the area of genetic testing is virtually never Level 1 evidence. Maybe every once in awhile, there will be something that can be done in a randomized controlled trial. The best quality evidence we're going to have is well-designed case-control studies, most likely, and some cohort data, and one of the things that the U.S. Preventive Services Task Force has begun to think about a little is whether you can take expert opinion and look at it systematically.

Expert opinion involves a lot of different elements, and if you use, if you look at the expert opinion in systematic ways that ties an opinion to the ancillary data that was used to generate that opinion, you can actually begin to rank expert opinion. So I would just say this kind of methodology may be extremely important for us.

DR. McCABE: David?

DR. LANIER: Just to follow up on that, many of you know that the agency now called AHRQ, formerly known as AHCPR, for a number of years was involved in producing guidelines, and we went through a near-death experience as a result of, from the Federal Government making recommendations for practice.

I think this is what Wylie's touching on, is the fact that now we've backed off and have what are called evidence-based practice centers for everything except the Preventive Services Task Force, and so what these evidence-based practices do is actually review all the available information, including expert opinion, and come out with a complete report about what the evidence says.

It doesn't say you should do this. That's then handed off to professional groups who then come out and

make the recommendations because the feeling is the professional groups have a great amount of power and influence in what their colleagues and peers would do without having the imprimatur of the Federal Government on them.

DR. McCABE: Elliott, and then Muin.

MR. HILLBACK: Yes. I think it's very interesting. I think one of the questions that we'll have to ask and come to grips with is whether we want to create a panel of some sort, a group that reviews these things or whether we want to create a process that takes some of these concepts and puts the onus on whether it's the individual lab or some organization to do that sort of review and be able to show that they've done it.

I worry particularly with some of the tests that have very small populations whether we're going to set up one group to look at this and end up putting a very long roadblock in the way.

But I do think the idea of developing some sort of a process that has a series of checkpoint controls in it is clearly one of the options we have to go on. Whether we want to centralize that or decentralize it is a fundamental question we're going to have to come to grips with.

Thank you.

DR. McCABE: Muin?

DR. KHOURY: I'd just like to follow up on this discussion this morning. The U.S. Preventive Services Task Force is a wonderful model to look at from all the points of views that were mentioned this morning.

I just wanted to elaborate a little bit on that. Most of what they take on or have traditionally taken on are issues related to clinical utility. Meaning, does aspirin reduce the risk of heart disease? Does chiropractic work for low back pain? And these are issues that are very important, and the recommendations affect obviously health care and preventive services.

When it comes to genetic testing, I mean, if you think about all the different kinds of data we need, along with the analytic stuff, which is mostly lab-based, and then the clinical validity stuff, a la penetrance, if it's a predictive test or diagnosis, that kind of intensive data collection that needs to happen at that level may or may not need the sort of the clinical utility analysis that would make a pronouncement at the end of the road.

I think before you get to the phase of making actual recommendations or discussing the pros and cons, you need to be able to gather the data on clinical utility which, for most of these genetic tests right now, that's where kind of the roadblock is. I mean, the clinical validity, the clinical utility is going to be slow to come. It will be hard to come by, but my own prediction is that for only a subset of genetic tests, where there will be a lot of controversy, a lot of discussion, it will reach a point where you have to have this kind of technology assessment that would lead into recommendations.

I think for the longest time, where tests have become introduced kind of slowly into a practice, and additional data get collected under the auspices of some group, then, for a selected few of these, you would reach a certain level of complex analysis or review to come up with these recommendations

because otherwise you will overwhelm the system with anything, and you have thousands of tests that will be coming down the pike.

So to recapitulate, I think we have to separate the processes of intensive review and technology assessment of the type that a preventive services task force can do from the original initial steps of the data collections or what Elliott would say, report to the public what we know and what we don't know, using systematic efforts, and then you can decide to either act on the data that have been accumulated or not act and let it float for awhile until it becomes ready for more intensive kind of discussion for policy recommendations. But for most tests, it will be that transitional period for a long time.

DR. McCABE: I think one of the issues is it sounds like this is a very deliberative group if they come out with a volume every six years. I don't think that's a model that we can adapt.

I think that the other one of the things that I've been thinking about, and I'll just throw out on the table, is the huge number of tests, and the fact that if we suddenly say you need to go through this process to be approved, if that's going to disenfranchise certain tests.

I think we've got to be very cautious as we come up with a mechanism not to have that happen, and we need to have a process, a group, whatever, to review what is currently available, and then also what we may have to do is try and, again using expert opinion, identify areas where we think there are problems and look at those.

So I think what's going to end up happening, and it's taking what Muin said and just restating it, I think we're going to end up with models because I think -- or we have to come up with a very streamlined process for taking what's already out there and dealing with it.

Pat, then Wylie, then Judy.

DR. CHARACHE: I'm struggling with the question of when is objective oversight essential? What are the checkpoints at which you need this type of oversight? And it seems to me that there are two different areas.

The first and the most difficult is when is a test ready to be used for patient care as opposed to research? When do the results go back to the patient or the patient's family as opposed to being part of data collection?

And then a second, an additional concept is what is the timing of this oversight review? If the CLIA model is used, the timing is ordinarily whenever the next two-year cycle is over and somebody comes to the laboratory. I'm not addressing competency of the person who comes to review it at this point, but it's a matter of timing.

The FDA model is that you review these before they get rolled out for patient care. If we use the FDA model, it's reviewed before it gets rolled out to patient care. This is where you have this very tight constriction site, and you lose opportunity over a period of time.

If you use the CLIA model, you really would have to have a surrogate method of ensuring that the test was ready to go out, and those surrogate methods could include a list of criteria that must be met, and the

criteria might be different for a low-frequency gene than for a high-frequency gene.

But I see the second advantage of this type of sophisticated consortium review being ones of assessing the data that points towards clinical utility a little further down the road, which is, I think, what Muin is pointing out as well.

So perhaps a combination of these types of thoughts might be put together. Specific criteria that had to be met before a laboratory would release a test for patient care, perhaps FDA review for tests of high-risk and high-frequency before it gets rolled out, which would be a small number that they could handle, keeping the numbers low, then oversight to be sure the laboratory had followed the guidelines that had been spelled out as being required before you release a test, and, finally, a consortium group that would be equipped to assess the utility over time.

DR. McCABE: Wylie?

DR. BURKE: I just want to speak briefly to the streamlining of the process issue. I think it's a very important point.

I do think that if we define a level of review that we consider as optimal but recognize that we can't do it for all tests, we need to be honest about that, and the test needs to be so labeled, you know. In other words, it needs to be clear at what level and to what extent it's been reviewed.

But having said that, I think it's worth pointing out that once you've created the structure and defined the kind of evidence that you want to have -- with most genetic tests, you're not going to have that evidence. The evidence review process is actually very quick. You know, it's more a matter of disclosure, and I think that's exactly what we've been saying all along, that that disclosure is very important.

So my guess is once we create the boxes that need to be filled, it will actually be easy to characterize most tests in terms of what we know about them.

DR. McCABE: Yes, Judy?

DR. LEWIS: I'm sitting here struggling a little bit with the idea of whether or not tests have to be valid before they can be released, and I'm wondering if something isn't valid, then how can you trust the information, and so the question that I'm sitting here struggling with is, you know, if it's not going to give information that's at all trustworthy, there could be as much right as wrong if it's not valid. Why are we ready to release it because we're not giving people information that they can trust?

DR. McCABE: Well, that was partly my point, that there may be tests that are already out there that would have this problem associated with them, and those, you might want to have expert opinion draw attention to them and rather than taking things in alphabetical order or whatever, historical order, whatever order one came up with, and you're going to crunch through them, say that there are certain of these that have to rise to the surface, and take a hard look at early on.

DR. LEWIS: Because the whole point is to give people something that they've got information. I mean, I think that's a disservice.

DR. McCABE: Barbara?

DR. KOENIG: I actually have probably a question. In addition to genetics, I do some work in the area of end-of-life care and have so gotten interested in the best practice kind of issues, and the one thing that that community is currently thinking about is a model, and there is obviously perhaps more data available in this area, although it's evolving, is the Cochrane Collaboration.

I'm just wondering how a model like that relates, if someone can tell me whether something like that is a possible model, or is it similar to the preventive task force, et cetera.

DR. McCABE: Can you tell us what that is, please?

DR. KOENIG: Well, I mean, I'm sort of hoping for some help.

DR. LANIER: Cochrane is an international organization of people that are very interested in outcomes-based research and pick a particular topic, either a treatment or a preventive measure, and just in very similar fashion to what the U.S. Preventive Services Task Force does analyzes the data in terms of the level of it, and again they use their gold standard, the randomized controlled trials.

DR. KHOURY: Can I comment on that?

DR. McCABE: Sure, Muin.

DR. KHOURY: I met with their executive group last year. They have an annual meeting where they review all kinds of studies, and as David said, they're primarily interested in clinical utility, sort of does Drug A work for Disease X, and we talked a little bit about clinical validity, and they're becoming interested in genetics.

So they're thinking of creating a field, you know. They have this elaborate mechanism where they have cross-cutting issues, like genetics or other things, and they have begun thinking about, for example, one of the projects they have is the clinical validity of testing for CCR5 mutation in relation to HIV infection and/or progression.

So this is sort of a penetrance-type discussion. I mean, if you are CCR5-positive, what would be the outcome? So it is a model not dissimilar from the U.S. Preventive Services Task Force.

DR. KOENIG: Except it's non-governmental.

DR. KHOURY: Right. It's purely academic.

DR. McCABE: Okay. I have Barbara, Pat Barr, Elliott, and Muin.

DR. KOENIG: I'm done.

DR. McCABE: Okay. Sorry.

Pat? Pat Barr.

MS. BARR: I guess in the conversation two questions have come up, and Judy sparked them.

One is, is it legitimate to call and ask the labs to call some of what they do when they put this out as research, but allow them nonetheless to charge for it, so that they keep their economic process going, but there are reviews about it until we are satisfied that it meets some standard of validity.

So we're not stopping their operation, but we are calling it what it really is and then having some mechanism to review it. So that was one question.

And then the other question is that if a lab providing service feels strongly about their right to do it within the mechanisms that exist because that facilitates the growth of information, is there a reason to not treat kits that are doing genetic tests in exactly the same way, and that is relieve them of some of the FDA approval?

It would just seem to me that we need one standard for the kind of examination that the patient is going to receive, and I don't understand at this point the distinction, except I do understand the distinction being that with a service, the lab has developed its gold standard versus the kit giving it to many labs, not knowing how well they'll produce it.

DR. McCABE: Elliott, you want to comment?

MR. HILLBACK: Yes, a couple of quick things.

To go back to Judy's comment, I think we have to keep reminding ourselves that really we're talking about a continuum. We talk about a test as if it's a finite point, and it really isn't, and so this process of knowledge, once a test is used once, we know a little bit, and when it's done 100,000 times, we know something more, and when it's done a million times, we'll know something more. What we're trying to manage is that continuum, and that's why this is such a sticky subject, and that's why the target of 100 percent clinically valid is a really difficult target to talk about when we do this.

So I think there is a fundamental level that you say there's no sense putting out a test if there's not useful information that comes out of it. Why would anybody do that? So I do think that we have to keep reminding ourselves that that's the fundamental hurdle that we have to make sure that any developer of a test gets across, is that there's useful information, and that there's some way to prove that it's useful information. Some documentation that says that.

Now, I agree with you that if there's not any useful information, there shouldn't be a test, but after some initial point, then you're talking about starting a continuous process that's going to last a long, long time. We're still eight years, nine years later, we're still doing that for cystic fibrosis, and we still have a long way to go.

DR. McCABE: Muin, did you have something to add?

DR. KHOURY: Yes. I just want to readdress that continuum a little bit. What we have right now, I mean, what Elliott said, is true. We have a continuum, except that it is a very haphazard and not-well-coordinated continuum. Things come in, and once they are entrenched into the health care system, data may or may not be collected basically, and sometimes governmental agencies, like NIH, step in, and they

say they want to do consortia and studies around hemochromatosis, but for many, many diseases, this doesn't happen.

And I think what this group can do is influence the process by which a test can move from the research phase into the being accepted phase which will have several components.

The first one, at the very minimum, is the assurance of additional data to be collected after a test is preliminarily approved, using some minimal standards, that data coming back, feeding back into the system, so that at any given point in time, as Elliott's favorite talk is, we tell people what we know and what we don't know, and then for selected few of these, we do more intensive types of studies, a la consortia, where original data can be collected or analyzed, and even for a selected few of those, you go to the final level of the systematic review when it's ready for this kind of consensus development or is it ready for prime time or not?

So that continuum from minimal data collection all the way to consensus development has to occur, and it will vary by test. It will vary by condition, but the missing link has been to the FDA and the CLIA piece, is this assurance of the feedback loop and having some kind of a national knowledge base essentially that says this is what we know today, and this is what we know tomorrow.

MR. HILLBACK: May I just amplify one thing here?

DR. McCABE: Quickly.

MR. HILLBACK: I think that we also need to remind ourselves, and I think that's what Muin just did, is that the generation of this information is a total health care system situation, because the people that are treating the patients, the people that are doing research on the outcomes, are the health care system, and what's really the most disorganized part, and we talked about it some yesterday, is the linkage between the lab data and the outcomes data that resides somewhere else in the health system, and I think that's a major place where we can play a role as this group to help reorganize the disorganized system.

DR. McCABE: Victor?

DR. PENCHASZADEH: I am just trying to follow perhaps what Muin just said. It would seem then that in terms of actual agencies responsible for approving -- I mean, that have the legal mandate and the power to say, to enforce whatever recommendations anybody will promulgate -- are the agencies that are already in existence, CLIA and FDA.

So if I follow what you're saying, what would really be needed to complete the picture would be all the management of information, the collection of data, and the ability to analyze data for essentially for the feedback and to ensure the continuum.

Now, but if that is so, then it would seem that such a body could be created in the model of the U.S. Preventive Services Task Force, but that would never have enforcement power. It would be a consultative body which will analyze data and will make recommendations. Who will have the power to enforce that?

Now, I've also been struck by what Pat Barr just said about two issues. One is a question of how do you

treat a test that is still on an investigational basis with respect to, you know, charging for the test and reimbursement issues, and whether insurance companies will pay for it?

Because I assume that there is no way out to have for a valid period of science, depending on which type of tests you have, tests that will still be investigational in nature, and I realize the need of test developers, if we want them to keep doing those research, to gather the data and so on and so forth, and there should be some compensation for that.

Now, the other issue that I'm still grappling with is the question of double standards between kits and home brews, and I think that is one of the things that should -- I would really argue for resolving that double standard because from the point of view of the patient, it doesn't matter how that test eventually came to be developed or how it's being marketed and so on and so forth. It's just a test that the patient receives, a patient or a population or whatever.

So, I wonder, I have been reading many of these materials and other things, and this eternal discussion, or the description, rather, of the FDA process for kids, it would seem that that process does give FDA a lot of leeway in deciding, you know, in expediting things for low complexity or lower class devices and so on.

And I would like to ask David Feigal, what has been the experience so far with that process, in terms of does it take too long? Are we really serving the needs of the development of tests, the needs of business, the needs of patients, and how that process could be streamlined in any way to accommodate all that we have been saying here and heard also in the public consultation in terms of not stifling research, expediting things when things can be expedited?

And just to close, I'm kind of concerned that the eventual guidelines as to what type of tests require more higher scrutiny be based only on the resources that are now available in the agencies that are doing it because that should not be the only factor.

I mean, if we decide, let's say, that they can only deal with a few, with a small load, perhaps instead of restricting the number of tests that will go to FDA, we should ask for increase of resources to do what we think should be done on the basis of objective criteria, not on the Federal Government's budget.

DR. McCABE: Steve, do you want to comment on the FDA and the kits?

DR. GUTMAN: Yes. Actually I have to comment on the last comment, which is, of course, in life, you get what you pay for.

I think it would be fun if people here who interact with the agency -- fun to see what their perspective is. We have clearly improved time lines over the last four or five years. We've clearly introduced new mechanisms for doing business. We've had a handful, a very small number of genetic tests we've actually either cleared or approved. A couple of them have gone to panel. They were by and large for somatic, not germ-cell changes.

But the truth is that we are, historically, more data-intensive certainly than CLIA. Even if you look at just our evaluation of accuracy data, where CLIA is going in and doing a survey, they have one poor reviewer who's looking at a whole lab, everything from the genetics test to the urinalysis lab.

We actually look at this stuff, and both Pat and Joann will certainly back me since they both know our process. We look at it from soup to nuts. We do take a lighter touch for some devices.

To be perfectly honest, the genetic tests aren't a natural fit for things we would take a lighter touch for for the reasons we have a special committee addressing them. So we have models in place. I think the models, frankly, might be more malleable than people think. The models would require us to do things that have been discussed this morning, to streamline, to shortcut, to shortchange, to look at labeling as opposed to intensive data review, to label things in an honest way.

If we were in fact to treat all genetic tests or even a moderate subset of genetic tests the way we treat our Class III or even our Class II devices, we'd just grind to a halt and chill the whole world of this technology, and I don't think that's really in the best interests of the testing.

I'm intrigued. I think Pat has taken a knife and gone right to my heart with her comments about the tension between the double standards, really a very telling and interesting comment.

We justify the differential treatment based on resources and based on the CLIA and that's only a justification. But I might say that there are processes. It is possible for investigational tests to have reimbursement. The reimbursement is theoretically supposed to reimburse only for costs. It's not supposed to allow the sponsor of the device to make a profit. We don't have any accountants on our staff.

So God only knows what actually happens, but in fact, the concept of paying for investigational tests that look promising is one that the agency has interacted with at least HCFA, and there are mechanisms for doing that.

DR. McCABE: Thank you.

Pat Charache?

DR. CHARACHE: I think the key break point in terms of going from a research test or patient care test is when you've established a knowledge base of the accuracy of the test for the population for which you're recommending it.

When you cross that line, you have a patient care test, and until you cross that line, you should not be offering the patient care because of the disastrous outcomes if you tell somebody they have a genetic disease when they don't as well as vice versa.

What is required now before you cross that line are things, such as you use the people who have the disease as the gold standard. What is the sensitivity? What percentage of those who have the disease do you detect? How many kindreds do you detect? Is this one family? Is it multiple families?

What is the specificity? You do match controls. How often do you say the gene is there when it's not? And then you get in to the laboratory practices. Is this set up as a laboratory which is not going to get contamination and say that it's positive when it's not? Is it equipped to handle patient specimens so that you don't switch patients? So that's when you're in the CLIA arena, and those are the things that are required.

Now, how do we achieve that in an efficient manner with the appropriate body doing that type of review, and that's where we get into, I think, issues, such as consortium training, back-up genetic capacity for whoever's doing it. We can say does someone have to send the data to a consortium versus the FDA? I don't know that's going to help.

You'll have people less skilled at reviewing than the FDA. So I would still come back to Steve with, can the FDA look at a subset of these that are of high need to review as opposed to having them all go through the same strategy?

DR. McCABE: Let me run through my list right now because I think we may be up against our time frame on this. But it's Pat Barr, Ann, Michele, Judy, Kate, Wylie, and Francis.

DR. COLLINS: Actually, I was hoping Steve would answer the question that was just posed before you go to the next one.

DR. GUTMAN: Yes. Let me interject because I actually think that Victor is right. I don't think the question is what the FDA can do. The question is what does this committee think should be done, and then you ought to challenge the Secretary and challenge the agencies to do what you think should be done. You should do what's right, not what we can do.

DR. McCABE: And I think, from listening around the table, that that is pretty much, I think, people had come to that conclusion, and that we probably will be recommending strengthening which will require resources, either new or redistribution, but again that's not really our issue. It's more to address what needs to be done to deal with these issues that have been raised.

Pat?

MS. BARR: I wanted to say two things. One is that while I understand very clearly that there's no endpoint, that is, we're constantly gathering information, for each patient who has the test, there's an endpoint which is the point at which that patient gets the result, and we are here to protect, I believe, the patient, so that at the time she or he gets the results, there is real meaning to that result and not -- and what we know, what we don't know isn't quite good enough.

The next piece I wanted to address is what happens out there really, and let's just take Herceptin, HER2/neu. I know in a small community hospital that every HER2/neu sample came back overexpressed. It was obviously a bad lab. They didn't know what they were doing, and I know that the variation on what the labs are doing and which academic labs set which standard for what is overexpression and what is not overexpression varied tremendously from lab to lab.

At the same time, to put a kit through for a HER2/neu kit was costly, elaborate, had to be reviewed twice, and yet from a patient point of view, creating a standard where we knew what assays everyone was going to use, and at what point the measure of overexpression was legitimate and not legitimate, was vital.

Now, is this a high-importance test or not? I mean, it was being used a lot, and it was being used by academic centers routinely for every patient running through their system.

DR. McCABE: Ann?

MS. BOLDT: Just practically speaking, in terms of talking about charging tests that are labeled as research investigational, there are many insurance companies that will not pay for that, and therefore it does become a deterrent for people getting those tests and having the endpoint that Pat was just talking about, and I really just want to echo everything that Victor said. I mean, I think we have to be concerned and mindful of those issues.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: Actually, Steve said what I was going to say. Asked for it. I mean, if you got what you want and then asked for it.

DR. McCABE: Thank you.

Judy?

DR. LEWIS: Pat touched on what I wanted to say, which is the point that I think we have two things that are going on in parallel.

One is the public health issue, and the other is the patient health issue, and I think those are two processes, and we can't ignore one. You know, one is looking at it from an epidemiological perspective, the other is looking at it from an individual perspective.

I think both of those are critically important, and the thing about for the individual patient making their treatment decision, it is an endpoint, was one of the points I was going to make, and I think the take-home message for me from the Baltimore meeting was expressed by Mei-Ling Chang, when she said we have to remember that the purpose of science is to serve people, and that we have to keep in mind what the goal of everything we do is, which is for the health care of people, and that we have to make sure that that's one of the goals that we keep in front of us.

DR. McCABE: Kate?

MS. BEARDSLEY: I was just going to say that it seems to me we've been talking really about a number of different things, and one is that we want to make sure that these tests have some level of clinical validity before they go into routine use.

Another is that we want to make sure that data collection keeps happening, and a third is that we want the information that's available to be all there and true, and I think what we're hearing from Steve is that if we try to put genetic tests through the usual FDA process of a Class III device, we aren't going to have any genetic tests for a long time, and that can't be a good thing.

So regardless of whether we put it through FDA in some other way or we don't put it through FDA, it seems to me that there's some sort of a trade-off between the three things that we're talking about.

If we're talking about requiring a lower level of clinical validity, then we ought to be talking about requiring a very high level of post-marketing data collection, and we ought to find ways to really push that data collection, and also if we're talking about a lower level of clinical validity, we also ought to be talking about a very, very high level of disclosure and accurate disclosure and try to balance a little bit the

fact that we don't have as much clinical validity as we'd like.

DR. McCABE: Wylie?

DR. BURKE: I'll speak to that point, too, but I really want to get it back specifically to Judy's comments and to Elliott's continuum.

I think it's instructive to think about an example like BRCA1. Linkage studies in high-risk families made it very clear that mutations in that gene were associated with high risk of breast and ovarian cancer, and it was reasonable to think about making a test available for such families.

But at the point where the test was made available, and I think we would probably all agree that was appropriate, we knew nothing about minority populations. We knew nothing about testing in women that didn't meet very rigid criteria for high-risk families which were the entry criteria for the studies. The test clearly had limited sensitivity.

I think it would have been reasonable to release that test with those caveats and perhaps with some concerns about informed consent concerning the limitations of the test even within high-risk families. That did happen. That is, those kinds of recommendations were made, and the test was released.

But what also happened very quickly after the test became available was the generation of recommendations, largely from respected professional organizations, suggesting that testing should be considered whenever there was a 10 percent or greater chance that a mutation would be present, and data largely collected in convenient samples and by the commercial tester defining family history characteristics that were much less strict than the original study families, suggesting when you might be able to define a 10-percent risk.

I think if we think about how we might like to see that kind of process go, the expansion of the use of the test is not necessarily unreasonable, but what we perhaps would have liked would have been an initial fairly strict indication being approved with the conditional use of off-label. That is, the conditional use would have been more data collection. That is, you can begin to expand to off-label use if you collect the data so that we can ultimately accumulate the additional clinical validity.

MS. BARR: And I just have to jump in, and in a reasonable way, so that rather than to go to the whole universe, you say step-wise, this is the next universe we're going to go to and then the next universe --

MS. BARR: -- and it should be a very simple, one would hope, design system, where you just come in and say this is the next universe we want to do, and this is the data set we'll use, and some period of discussion about the appropriate data set.

DR. BURKE: And that can be planned. That can be planned at the point that the test is initially released.

DR. McCABE: I think there are a couple of important points here. One is the term "conditional" as opposed to "investigative," because this will make a huge difference in terms of reimbursement.

I think the other point really has to do with off-label, and the fact that, you know, whether you call it conditional or whether you call it off-label, but that basically if there is a good faith ongoing effort to

collect data, that then has some sort of special situation within the system.

DR. BURKE: And can I just add briefly, that it seems to me something we could accomplish or the process we develop could accomplish, is a definition of the data. It's not just a good faith effort to collect data, it's this kind of data that we need.

MS. BEARDSLEY: And in this time frame.

DR. McCABE: Pat?

DR. CHARACHE: Can I jump in and say that our recommendation should strongly include the request that the congressional mandate that the FDA cannot look at off-label be removed?

DR. MCCABE: Elliott? No, I'm just thinking --

MS. BARR: I wonder if it's going to be easier for us to call it something else and then hope that that will be done later, only because of our time frame and because we'd like a system in place.

DR. McCABE: Given the current relationship between the Administration and the Congress, I think that while it's a nice windmill to tilt at, I'm not sure it's the one to take on.

DR. CHARACHE: Well, I would just like to be sure that we say the windmill is there.

DR. McCABE: O.K., Elliott?

MR. HILLBACK: I guess the other comment along these lines is that remember we're again talking about the whole health care system. So that once a test is available at a laboratory, a prescription by a physician says I want to do this test, and we begin getting test requests, I think most laboratories actually kick back tests and say we're not sure this is appropriate, but you get into a very difficult situation again, and so I go back to a point that we've said we will defer until after this point, but we have to keep in mind that I think there are three fundamental issues that this committee's going to have to deal with.

One is the privacy/confidentiality, reduce the concern of the populous about the improper use. One is what we've been talking about today, which is how do we introduce a test properly and well, and the third is, how do we make sure the people that are using those tests understand how to use them, so that we really have an integrated system of genetic care, genetic-based care?

And until we have that other side, we can do all the things at the lab end we want, but we don't totally manage this whole issue of how is a test used, when will it be prescribed, when will a sample show up, saying please test this sample because, and, you know, I know people believe that the sales force of our laboratories can change the world, but you give them much too much credit most times.

So I think there is an issue that we have to manage that is much broader, and I know we're going to come back to that as a committee later, but we can't forget it because it does drive what happens.

DR. McCABE: Pat, and then we're going to move on to the next question.

DR. CHARACHE: Just one last comment. I think, unfortunately, the Notice of Intent was not discussed here that has gone out by CDC, but this is one of the directions that is being pursued, a requirement that the laboratory not do a test if it's not appropriate for the request, and this is going to require a lot of thought and a lot of comment, but it's along the lines that have been suggested, and I have no idea whether it, where it will go.

DR. McCABE: Could you clarify what the Notice of Intent says?

DR. CHARACHE: Yes. The Notice of Intent is the outflow of the Genetics Working Group under CLIAC, and it did address the pre- and post- as well as the analytical aspects of the test with specific requirements.

Among the pre-analytical requirements was that for those tests which were defined, and this was a consortium concept of who would define it, that it would be defined if they need signed consent, that the signed consent be obtained before the test was performed.

If it was necessary to have clinical information in order to interpret the test, that that information be provided before it was performed, and that the laboratory not do the test if the pre-analytical requirements were not met. They stabilized the sample, put it in the freezer, whatever, but not run the test if they couldn't interpret what came.

The post-analytical included information that was necessary to use a test, which included much of the requirements that this group has defined. What population? What is the meaning of this test that's being returned?

So there's a lot of what this group has talked about that's in that Notice of Intent, and I think it would be extremely helpful if the committee gave its views individually, if they wish collectively, on the strength of that approach.

Some of it would be difficult to implement, including the issue which Elliott just raised. If you know that fragile X is not what you should be looking for based on the clinical description that is received, then it's the responsibility of the laboratory or its genetic counselor to contact the physician and make sure that the appropriate test gets performed or does not get performed on a population that's incorrect.

MS. BARR: Does that happen in regular medicine?

DR. CHARACHE: This is a new thrust of the CLIA initiative. It's in the regulations. It's certainly in the law, but it's also in the regulations, but they've not been enforced, and that's the importance of this Notice of Intent.

DR. KHOURY: Can I respond to this since this is a CDC issue?

DR. McCABE: Okay, Muin.

DR. KHOURY: Pat is raising probably the most complicated aspects of the Notice of Intent, and obviously the one that deserves most discussion and probably most input from the public because if that's implemented in its at least current philosophy, it's basically tantamount to the regulation of the practice of

medicine, and we've heard concerns from people about those issues, and I for one -- you know, I think it's going to be very difficult for that implementation.

Having said that, however, I think a lot can be put on the labs, on the shoulder of the lab director as the gatekeeper to make sure that things are moving smoothly, but to have, you know, all the issues about clinical validity and clinical utility as a prerequisite before you do a test is going to be extremely difficult to implement.

DR. McCABE: Yes. I think there is a model here, though, and we need to recognize that this is one of the differences between genetics and others, and that's maternal serum alphafetoprotein. If you get an MSAFP with no data on the pregnancy or anything else, you can't interpret those data.

I mean, it is a fine line between regulating the practice of medicine but also ensuring the quality of the information. One of the big problems in medicine is that clinicians don't provide laboratories or radiologists or others with the clinical data, but here is a case where you really can't provide a result for a lot of these without the data.

Reed?

DR. TUCKSON: Yes. Let me just make sure that I understand this. Given the implications of this Notice of Intent, do we need to pay attention or respond to that in the report? Is this something that's going to fundamentally change any of the landscape or the foundation from which we are working or should we simply be aware of it, and our recommendations will be our recommendations, and hopefully whatever this is, if we disagree with it, will not be implemented?

I mean, we're recommending to the Secretary. I just want to know how specific do we need to deal with this as a foundation issue.

DR. McCABE: Pat, and then Elliott, and then we're going to wrap this up.

DR. CHARACHE: I think the Notice of Intent will be 100 percent compatible with the goals and directions of this committee.

I think that the understanding of this committee will be very helpful in moving the laboratory testing in directions that it should go, and there are laboratories that won't do a test if they can't interpret it. There are others that will do anything that walks in the door.

There are many laboratories, 70 percent, that have a requirement for signed consent for specific genetic tests, and according to the JAMA article, 7 percent of them follow their own policies.

So I think there are a lot of opportunities here and a great deal of strength in moving in some of these directions.

DR. McCABE: Just to clarify, we have not endorsed the Notice of Intent. What we requested was acceleration of publication of the Notice of Intent because we felt that if it got into a queue behind what we were doing, that that was a disservice. So we have not endorsed it, but we have requested accelerated publication, and that is moving ahead.

DR. TUCKSON: Is it possible we could get a copy of that again? It's not in our packet. Can we have it during the lunch hour, maybe?

DR. CHARACHE: I am not recommending this group do -- I mean, you've not seen it, and there obviously may be pieces of it that individuals like and other pieces that you won't.

DR. TUCKSON: No, I'm just concerned for the very reason that the chairman just mentioned, that we asked for it to be accelerated, is, I mean, if you have obviously something that's this specific to what we're doing to parallel with our recommendations, and the timing of all this, I'd hate for us to not be aware of it and not respond to it or reference it in some way and say this is either consistent or inconsistent with where we're ultimately going to come out. But to ignore that there's this parallel track, I think would be inappropriate.

DR. McCABE: Judy, are you following up on that? Please.

MS. YOST: I do want to mention that I think it's extremely important that this group understand what it is in that Notice versus the discussions that are taking place right as we speak now because I think that information has got to dovetail together, and I think that it's important that even with whatever recommendations you come up with in this process today, because I know that there is a deadline for report back to Dr. Satcher, that you be aware of this and in some way at least indicate the presence of that.

It's unfortunate that the clearance process to get the notice out through CDC -- they've done the best they can. I know they have worked very hard to get it through the system. Unfortunately, it's not going to meet your March 15th deadline to be out and then have a 60-day comment period and have those comments compiled, and I think that's a very unfortunate circumstance because I think that the public comment that comes in from that needs to be clearly part of the final recommendations that this group would make in some way because you're going to get a whole different audience perhaps to that because that impacts the whole CLIA program, not just but genetic testing because CLIA is every test that's performed at a clinical laboratory.

So you really need to think about the big picture in the laboratory as well as what you're doing, but I think you really need to think about the timing and your knowledge, your in-depth knowledge, of what that says, so that whatever you come up with fits together with where that is going. Otherwise, somebody has to go back to the drawing board because it may not work.

DR. McCABE: Elliott, can you be brief, please?

MR. HILLBACK: Yes, I can. I just wanted to second what you said a minute ago, reminding us again that patients are why we do these tests. If you don't have the information about the patient to analyze the situation and to provide an adjusted risk or whatever it is we're going to provide back through our counselors, you can't do the test.

So you said it very well when it came to prenatal testing. It's the same for DNA testing. If certain data isn't there, it's just impossible to do the test, and we would be totally -- I don't know what nasty word you want to think of. Just wrong to do it. So we don't, and I don't think most labs do.

MS. YOST: No, they don't, and that piece has always been a part of the CLIA requirements. CLIA

always said whatever information that was pertinent to that laboratory performing that test needed to be provided in order for the laboratory to continue the performance of the test.

What that notice does in some cases is just perhaps reinforce that a little bit, but clearly it brings it closer to the borderline when you talk about the appropriateness of the test with the patient diagnosis, just brings it a little closer to the practice of medicine and where the physician decides when and where and what tests he's going to use.

The laboratory, I think, clearly has to play an important role in sharing with that provider what they need to know about the test, and that's where I think part of this group can provide that guidance.

DR. McCABE: Okay. With that, I'm going to move on to Question 5. So Susanne and Alan, could you discuss this, please?

DR. HAGA: Issue 5 was what is an appropriate level of oversight for each category of genetic tests?

This issue had the lowest response rate from both my half and Alan's half, and either it was difficulty in understanding the question or the public was just at a loss of what to say.

So the responses did tend to group into three areas. One was to expand CLIA regulations. The second was that other government agencies should have oversight for each category of genetic tests. Higher oversight would be necessary for higher impact. Riskier testing. The suggestions were FDA or NIST that came out.

Overall, the responses were extremely variable. There was no favorite. There wasn't a clear answer, but education did come through. Education on the part of the provider, education on the public side, the consumer side, and counseling were always mentioned, and that that would be appropriate for each category of genetic tests.

5.1 was how can oversight be made flexible enough to incorporate and respond to rapid advances in knowledge of genetics?

Again, the responses were extremely variable and extremely few. An establishment of a committee of some sort of stakeholders, including consumers, seemed to appear most. The committee approach would be most flexible. They would most likely be able to respond in a flexible manner to advances and changes in technology and information. They would be able to consider more of a broad range of issues, that CLIA was more focused on laboratories, and that a committee may have the ability to readjust its focus to other areas.

Another thing was the committee would be able to establish guidelines in a more timely manner, and they could readjust those guidelines as they saw fit, and it would be an ongoing evaluation process, that it would not be a one-time review. So that would again take into account the changes in information, and CLIA was cited to be a very flexible system, that it would be better than establishing something totally new, and again it would be more flexible.

DR. McCABE: Nothing to add, Alan? Okay.

So let's open this up for discussion. Yes, Joann?

DR. BOUGHMAN: I'd like to do my selective survey of public comments here that I think fit with the discussion that we've been having.

One commenter said, "The issues related to genetic tests cannot be separated from the issues related to the provision of such tests. In other words, gene testing and the assessment process that should be a central part of the federal oversight independent from the test sponsors."

In other words, acknowledging that the performance of the test and the pre- and post- aspects are critical.

One of the organizations here said, "Major concerns about oversight of genetic testing for this certain cancer relate to clinical issues involved in the ordering and interpretation of those tests."

And then one of the companies made the comment, which just reaffirmed this from a slightly different point of view, "Most of the questions we receive in our company from client health care providers and patients relate to translation and interpretation of the genetic information in the medical reports."

So even if there is the appropriate information provided at the point of testing, when the test is done, they're still getting questions, and in fact, that's their most question -- what does this really mean? Now that I've got the report, and I gave you all the data, what does it really mean?

And one more that I think just may weigh as heavily on other people's shoulders as it did on mine, and that was a general comment, "Genetics is in the forefront of legal and ethical problems that are soon to be shared with all of medicine."

In other words, we in fact are grappling with exactly these standards of care, standards of practice issues at the front end of the curve, and that what we have to say may have a great deal of impact.

This also fits in with Barton Childs' recent presentations at the AAMC and at a Pew conference in which he talked about viewing medicine through a genetic lens, and that in fact, the future of medicine is genetic medicine, and that there are no physicians being trained today that, during their practicing careers, will not be in fact practicing genetic medicine, which I think puts it all in perspective.

DR. McCABE: Yes, and there's been some discussion, people. We've had some of the respondents who have said there is no difference between genetic testing and other testing, and I would argue that that doesn't really matter in our deliberations.

The key thing is that we know what genetic testing is, and apropos to your comments, I think if we set a model for other testing, then we've done a service to the people.

Other discussion? This one's going to be easy. Pat?

MS. BARR: It just seems to me this one is the last one. I mean, so, if we could get perhaps more specific in terms of really talking about should there be an independent body before it goes out the first time? What should the standards be, and then which agency should oversee that, and what are our goals?

I mean, I actually, as a consumer rep, have two clear goals. I want the tests used appropriately, but I really do not want to slow this process down to the detriment of the people.

I'm willing to slow it down some, so that we get tests used appropriately, but I think it's a balancing, and I think that's the discussion. What's the line? If it's appropriate for high-risk patients, it should be out, but how do we get it then? What's the next step, so it's not abused?

DR. McCABE: Yes, Joann?

DR. BOUGHMAN: I would also suggest that one of the reasons that the public did not comment in the same way about this one is that the way the question was worded was how would you tie together your suggestions in Number 4 with the proposed categories, and a lot of them didn't like our categories, to begin with.

So they were in a dilemma of, all right, do I answer it my way or your way and decided I don't know, and I think I've given you what you need, and indeed I think they already have.

DR. McCABE: Wylie?

DR. BURKE: I'd like to follow up on Pat's comment, but I think it's relevant to Joann's, too, and that is that it seemed to me these answers provided us with a menu of choices, and we really need to figure out how to translate discussion around this point and discussion that we've had up to this point in to the beginnings of a pattern or a program, and what I think we probably need to do is to begin to define the steps along the way.

What we've just started to discuss, the steps along the way from the first laboratory evidence that a test has clinical value to what we might consider a lab test that has all the validated information that we would like to have and ask what actions need to occur at each of those steps.

I think that's what Pat was just starting us on; that is, what kind of review needs to happen before a test comes to market? What kind of limitations could we imagine being imposed given the kind of data that's likely to be available at that point? How does that data get collected, and what kind of review process occurs? That's one parallel issue. And how is the actual implementation of the lab test supervised?

I think if we could walk through and maybe begin to actually define each of those points, we're then in a position to say what existing agencies and activities match with things along that pathway that we would like to see happen, and what actions that we would like to see happen don't yet have an analog in the current system, and I think if we did that, we'd find that we already have a lot of the pieces, and there's a small number of linking pieces that we need to create.

DR. McCABE: Judy?

DR. LEWIS: I want to underscore what Wylie just said because what I was going to start out by saying is rather than starting with the agencies and what they're doing and putting together a system, let's figure out what we want and then figure out where to get it done, rather than start with what we've got the capacity in the system to do because then what we do is we're just creating a different kind of patchwork.

But I'd rather see us come up with a process and then figure out how to implement it or have somebody else figure out how to implement it by where the capacity is or where we need to create a new event, but to make sure, and to me, the critical pieces are that it involve, you know, providers at all levels, the lab, the health care provider and the consumer.

DR. McCABE: Pat?

DR. CHARACHE: I would also like to strongly support that. I think it's an ideal way to go, and I think then not only can we explore which particular agency is best equipped to handle a given area where the consortium concept would fit in very helpfully, but what are the missing links? What are the other things that have to be developed?

DR. McCABE: Is that how we will proceed then? I would ask Sarah to have one of the staff -- rather than having, you know, one of the things to write on, the paper to write on, I think we can do it on overheads, and everybody will see it more easily. Or the computer, whichever people would prefer.

MS. CARR: Do you want to do that now?

DR. McCABE: Yes. Why don't we get started with that? Because I think we're all feeling some urgency. Yes. So if we can set it up with the computer to begin to put in what some of these characteristics -- so, Wylie, do you want to start going back over some of this?

DR. BURKE: Well, I will make a few comments, but I think I want Pat to comment, too.

It seems to me that at the very front end of the process, we have a transition from laboratory data to clinical delivery of a test, and what we have is knowledge on the part of people doing a certain body of research that there is enough clinical validity and enough ability to systematically assess a particular genetic entity, that it's reasonable to offer it commercially.

So basically, we have a group of people who have some knowledge that they want to use to make a case for commercial development, and what I think we've already discussed fairly clearly is that we would like to create a structure into which that information gets put.

In other words, there's a series of questions that the person who's proposing the commercial use of the test needs to answer satisfactorily for approval to occur.

I think there are two questions that come up when we agree that that's the general process. Question Number 1 is -- I'm sorry. Maybe they're the same question because Question Number 1 was what agency does the sign-off, but I think Question Number 2, obviously very tightly correlated, is who does the review? Who does the review, and I think that's where I'd like you to speak, Pat. Is that, should that be an independent review or independent of the agency that's signing off?

MS. BARR: I actually would like to engage Elliott on this, and I'm hoping that Elliott will be -- now, Elliott, don't think about your lab, which let's all presume does it right.

Let's think about the very large number of labs that do not do it right, and what is the nature of the independent review, because I think there should be an independent review, and I don't want to give it to

an IRB that doesn't understand genetics, that would do the kind of assessment that you say you do in your lab, that would do it quickly, and that would then give us a good way to give to the appropriate agency the right insert that goes with the test, because that's really what we're talking about.

Who should this test be for right now, given what we know, and who should examine that? Because I'm going to assume there's good research, for instance, the high-risk, the BRCA1 research, and so therefore, we should make that available, but we don't want it to expand it.

So who should be the group that just looks at that research and says check off, we're ready to go? It shouldn't be myriad.

DR. BURKE: And if I can just interject, it would be with a template. In other words, it wouldn't be that that group putting data together in whatever format they want. There would be a preset format into which data has been put.

MR. HILLBACK: Again, I think, Pat, one of the things you're assuming is that this is a proprietary situation, and I think we ought to take the other situation, which is probably more likely, which is research is done by a group of treating physicians that say we found a correlation between a mutation and a gene and some outcome in a patient, and now 20 laboratories, including Mayo, Baylor, Genzyme, and 10 others, 17 others, all say, we've seen this correlation. It's in print. We need to gear up to offer this test.

There's no one lab that's got control of this gene. It's a gene in the public domain or Celera owns it instead of Francis owning it. Sorry, Francis. No, it's in the public domain. There's no issue about that. There's two or three peer-reviewed papers that talk about this correlation, and now there are going to be 20 or 30 laboratories, maybe 10, that say, okay, there is enough information that I can take that information, and I can now provide a useful service to a small subset of patients, and as we know more, I'll do more.

I think that's the more normal situation than the proprietary situation where some lab owns a mutation or thinks they own a mutation and is going to, you know, say we're going to develop something. We've done all the clinical research. We've been out, you know, watching the patients get treated, and now we have something that's totally unique in the world.

So the process has to be, you know, here's data that's available in the public domain. It's been published. We're going to do first our analytical validity work, and at the same time, we're going to then run various positive and negative controls through our system, and our genetic counselors are going to get up to speed on what the situation is, and at some point, we're going to be comfortable that there is useful information to provide here, and we will offer the test clinically.

I think you ought to stay away from commercial again because it's really the conversion from research to clinical practice. Forget the word commercial. There are lots of laboratories that do this on very rare diseases that move into providing the information for clinical use.

I think this is the process we ought to think about that's more likely, and I think will be increasingly likely as more laboratories decide that DNA testing for this, that, or the other thing is a useful thing to offer to their patients.

Certainly for a lot of prenatal tests or a lot of non-genetic tests, you know, many, many hospitals in the country, hundreds, are probably doing tests that are not genetic at this point.

So I think if the future of genetic medicine is that, that hundreds of hospitals might be doing these tests, how do you do that? They're not necessarily interested in buying kits. You can buy the primers. You can go through the ASR process and look at the primers and develop a test, and it's uneconomic to jump through a big hoop to do it.

So the other alternative is that you say, well, I only want two people to do it, and so we'll make it very difficult to get through this loop. We'll make it expensive to get through this loop, and we'll have, you know, the Genzymes and the Baylors and the Mayos, the large genetic testing labs in the world, and Quest, some of those people, be the only ones that can afford to do it. So I think that's the reality. I'd welcome comment if people disagree with me, but --

DR. BURKE: But I think even if that's the reality, the question is what would happen next? You know, in other words, to take the scenario that you outlined, which is the data's in the public domain, a lab decides they want to deliver the test, they need to provide some evidence about their ability to provide a high level of analytic validity, they need to provide a rationale clinically for doing the test.

MR. HILLBACK: That's right, and it's provided -- remember that every lab -- every result is signed out by a geneticist, and the decisionmaker is that geneticist saying can I sign this case out?

DR. McCABE: I want to start capturing some of these because I want to start getting concrete, and then we can start editing these concrete remarks. So let's talk about the research phase.

Susanne or someone's going to be typing in up there, so it will appear on the screen, but there is the research phase, and I think everybody would accept that during the research phase, you need to establish analytic validity. Okay?

You know that you can do the tests, and you can do it reproducibly. We just heard that you also needed to establish a rationale for clinical application because just because you can do the test doesn't mean you should do the test out in the world.

Anyone wish to debate with those things?

MS. BARR: Just subset of rationale for clinical application is also appropriate population.

PARTICIPANT: Well, part of it.

MS. BARR: It's part of it, but I think we ought to be clear, because that's a question that comes up in the universe.

DR. McCABE: So under that, a sub-bullet is to establish the population in which it is appropriate to do the testing.

DR. CHARACHE: Also, as a subset of that, can be stipulate what we're talking about is the sensitivity and specificity for a given population, because we get into verbiage confusion.

DR. McCABE: So establish population --

DR. CHARACHE: Sensitivity and specificity.

DR. McCABE: Okay. So sensitivity and specificity.

DR. LLOYD-PURYEAR: Wait. You don't know that yet, do you?

DR. CHARACHE: Yes, you have to, before you can do a test for that population.

DR. KHOURY: Can I say something here?

DR. McCABE: Muin?

DR. KHOURY: Yes, I think you can do that for diagnostic purposes, but when you're talking about predictive purposes, it becomes more difficult. You're trying to establish the penetrance of BRCA1, and that you may not know at the outset. But you can know the proportion of breast cancer cases that have a BRCA1 mutation. That's your clinical sensitivity on a diagnostic basis. But for predictive, it's difficult.

DR. CHARACHE: No, I didn't say utility.

DR. KHOURY: Well, that's not utility. That's still validity.

DR. CHARACHE: Okay.

DR. McCABE: One of the things I wanted to do was we were soon going to bifurcate or maybe more than bifurcate this pathway. So why don't we strike sensitivity and specificity, because there's some discussion of that. Then at some point we're going to need to start establishing that there may be different types of tests, and the question is have we already reached that point.

DR. CHARACHE: I think that it would be important to be clear on this. I think Muin is right. I think you should say the sensitivity and specificity for the use that you're proposing for that test. So if it's coming out as a diagnostic test, you need to know that. If it's coming out as a predictive test, you need to know that.

DR. McCABE: So let's now begin to look at the types of tests, and we can use a variety of different types of tests.

Wylie?

DR. BURKE: Just following up on that point, on Pat's and Muin's point, I agree with the point, but I think we need to be -- and maybe it is different categories -- we need to be very clear that we simply cannot know sensitivity and specificity, particularly we cannot know the predictive value of a test that we suspect is associated with susceptibility. So the BRCA1 example is very germane here. You might well, as Muin said, be able to define what proportion of people carry BRCA1 mutations. You have good reason to think there's an associated increased risk, but you simply don't know what level of risk is associated.

DR. McCABE: Okay. Let's move, and let's start, then, again if we talk about some of the accepted criteria or testing types in genetic testing, going way back to 1975, but they still hold up. That is that there is a correlation, a direct correlation, what we would refer to as a simple Mendelian trait but we know now isn't so simple, but the simplest of Mendelian traits that we could come up with, where there appears to be a relatively close correlation: if you have this mutation, you have a disease. So that would be Category 1 from the National Academy of Sciences panel back in 1975.

MS. BARR: You have or you are going to get in terms of symptoms, or do you not care?

DR. McCABE: Well, you could argue that for PKU, then you don't have the symptoms, but you are going to get the symptoms.

MS. BARR: Well, I'm thinking about Huntington's, which is that kind, and you carry it.

DR. McCABE: Yes, but that's predictive. I want to go to even the simpler, that it's a diagnostic test, pure and simple, and if you have this you are going to get it, and it's going to be relatively close in time. Okay?

MS. BARR: Yes.

DR. McCABE: Yes, Judy?

DR. LEWIS: So where you're leading us to is rather than looking at Mendelian, we're going to look at diagnostic tests, then we're going to look at predictive tests?

DR. McCABE: Right, and we're going to look at predictive. Yes, right.

DR. LEWIS: Okay. I'm just trying to be clear about how we're going to separate out.

DR. McCABE: How does the committee want to do this? Do you want to go through the examples one by one, or do you want to delineate the examples?

DR. LEWIS: I'm just trying to get a sense of what the categories are.

MS. BARR: Let's see if we can agree on types.

DR. McCABE: Okay, so types. The second --

Francis?

DR. COLLINS: It seems to me where you're leading is three types of categories, and I'm taking Elliott's comment from yesterday, that we don't want to go beyond three dimensions or we're going to have trouble thinking about it. But it's going to be hard to have less than three from the way you're starting this off.

One is diagnostic versus predictive. Another is Mendelian versus non-Mendelian, highly penetrant versus weakly penetrant is maybe a clearer way to say it. The third one I think we're going to have to wrestle

with is, is an intervention proven to be valuable or is it not? So I propose those --

DR. McCABE: Can we try to capture those? Do you want to do them again for Susanne, please?

DR. COLLINS: Diagnostic versus predictive. The second one is what you already started to do, which is Mendelian versus non-Mendelian. But let's say highly penetrant versus weakly penetrant.

DR. McCABE: Yes, I think that's better terminology, really.

DR. COLLINS: And then proven intervention available versus not available.

MR. HILLBACK: These are axes, right?

DR. COLLINS: These are axes.

DR. FEIGAL: Do you need one for severity of condition versus not?

DR. McCABE: You weren't here yesterday, but one of the things we discussed is that as we get into those sorts of issues that are defined by the individual, it gets hard for a group to come up with this. I think what Francis has done for us is that he has defined some axes that really we could use scientific criteria, expert opinion to place tests along those axes.

Wylie?

DR. BURKE: Also commenting on the severity issue, it seems to me we had some fairly cogent public comment that argued moving away from our arbitrary categories about severity, and I think Judy's comments yesterday were important, too. That is, there may be too much subjective judgment in making rigid categories between what we might call severe or less severe.

DR. McCABE: And also, I think what Francis has done very nicely for us is set axes, so that each of these is a continuum, as opposed to being a category per se, so that they really do make nice axes. But we need to discuss them a little bit more to be sure we agree with them.

Pat Barr, then Pat Charache.

MS. BARR: I think this is addressed, but I want to be careful that the pharmaco -- what's the right word? -- genomics are in there comfortably, and I guess they'd be coming forward with proven intervention available, because that's the whole justification of what they're doing.

DR. McCABE: Right.

PARTICIPANT: But they might well be weakly penetrant.

DR. COLLINS: Or they might be highly penetrant, depending on the test.

MS. BARR: But there's a place to put them in.

DR. McCABE: But again, these are axes on which you would then choose where an expert panel or individual, presumably panel, would then place where you thought that fell and come up with it in a three-dimensional space.

Pat Charache?

DR. CHARACHE: I just want to be sure that the group has either voted this in or out. There was a question raised a number of times in discussion about gene frequency and disease frequency. Would that be addressed under each one of these, or would that be ignored?

DR. McCABE: I think that that again, I think gene frequency is a category -- I would see gene frequency as a criteria perhaps for review, but not necessarily one of these axes per se.

Barbara?

DR. KOENIG: I just am not totally clear how screening fits into the first category. I understand that it's in the predictive category, but my sense has always been that predictive testing versus predictive screening are quite different in terms of how they work out. But I just wanted to raise does this include screening adequately.

DR. McCABE: Well, I think that screening can be diagnostic also. You can be screening in a population for diagnoses. I think we, you set your parameters differently for screening than for diagnosis, and we have to recognize that screening tests will be different than diagnostic tests. The screening process is different than the diagnostic process.

MS. BARR: But isn't this another one of your criteria for review? If it's being done for screening, it might have a different criteria for review than for individual, in the same way that we talked about phenotype/genotype.

DR. McCABE: So let's start a criteria for review, then, so that we capture these. One criteria for review might be, we've discussed is frequency. Certainly, if something is very frequent, you might want to think about it sooner. That's really up to the panel.

The other criteria for review was population-based screening versus individual diagnostic testing, recognizing that now we're talking about the purpose as a criteria for review.

MS. BARR: It should be.

DR. McCABE: Okay.

Yes, Judy?

DR. LEWIS: I just want to make sure that under "Diagnostic versus Predictive," we are including symptomatic versus asymptomatic. Is that fitting in there?

DR. McCABE: Right. Symptomatic would be diagnostic, asymptomatic would be predictive I would think.

DR. LEWIS: I just want to be sure that we're capturing that piece, because that was one that we heard a lot about.

DR. McCABE: Wylie?

DR. BURKE: Actually, I was commenting, my comments were to the criteria for review. It seems to me not only frequency and screening versus individual testing, but also a number of social factors that we've discussed, whether a specific population is addressed, whether there are special concerns related to potential for stigmatization.

DR. McCABE: Okay. So how do we want to capture that? Do you want to give us some specific examples?

MS. BARR: The ELSI concerns. And that's sort of a wrap-up.

DR. McCABE: Okay, so ELSI concerns.

DR. LLOYD-PURYEAR: That's a little broad.

DR. McCABE: Well, but in terms of a panel making a decision, I think the point is that if there are major ELSI concerns about stigmatization, that that then rises higher in terms of need for review.

DR. COLLINS: So why not call it stigmatization? I'm a little worried that ELSI concerns means a million things to a million different people.

DR. McCABE: Can we go back to , can we go to stigmatization? Are people happy with stigmatization?

DR. BURKE: And defined populations. I think they are two separate issues. Testing targeted to a specific population.

DR. McCABE: Okay. So stigmatization, potential for stigmatization, recognizing that all of these are potentials until one does them. And then I want to capture before we go on, I want to capture the other point that Wylie made, which had to do with populations --

DR. LLOYD-PURYEAR: Targeting populations.

DR. McCABE: Well, is it the targeting of, or the target population?

DR. LLOYD-PURYEAR: The targeting of.

MS. BARR: Don't we always have to target? Because that's what we're talking about, making it appropriate to the appropriate group. So it's the nature of the targetization, isn't it?

DR. McCABE: Interesting word, "targetization."

MS. BARR: Well, it's the nature of the targeting.

DR. McCABE: No, I mean it was very appropriate. I also feel that that really hasn't captured quite what the issue is in terms of criteria for review. Since the issue is if there's potential for stigmatization, that might involve specific populations. I think that's the concern for review, that the nature of genetics is that you need to determine whether it's an ancient mutation or a recent mutation, and that will determine whether you do it in everyone or you will be limited by the nature of the subpopulations that you examine. But that's not a criteria for review, really.

DR. CHARACHE: Is it stigmatization of target populations, versus stigmatization of individuals?

DR. McCABE: It's both, and I think that's captured under potential for stigmatization.

Barbara?

DR. KOENIG: If this is my only chance to get in social criteria, I'm not willing to leave it just to stigmatization. I sort of like the big ELSI category a little better, because then it was at least still on the table. But the other real issue that we're going to have to address at some point is the medical/non-medical and how to deal with that. And I had one suggestion which I just want to throw on the table now as a way of dealing with this, because it's such an incredibly complicated issue.

In the reviews of the international material, it mentioned -- and Susanne, I tried to get some clarification from Susanne but she couldn't help; perhaps other people know -- that in France, for example, they simply have developed a policy, if this is true, and I'm not totally clear yet, that they simply are not at this point allowing non-medical or non-legal uses of genetic tests. So I think one of the things that we're going to have to grapple with is if we're choosing it, we're saying that we can't at this point deal with oversight of non-medical tests, then perhaps at least put on the table, even though we recognize that there's no clear line between medical and non-medical uses of genetic tests, at least to start with that and say that at this point we want to have the issue of whether it's medical or non-medical be a criteria for review, and say that our recommendations for oversight are really only for medical criteria and that we'll be examining others later, and that we recommend basically that the others not be allowed into the marketplace at all at this point.

I'm sorry, I'm being very confusing. Help me.

MS. BARR: No, just what's non-medical.

DR. KOENIG: These would be things like tests for blue eyes or behavioral sorts of things, tests for violence, those kinds of things.

DR. McCABE: This is something that the committee needs to discuss, but as I'm hearing this, the issue is do we want to say that we can't get our arms around everything, that we need to at least develop a model, and that we need to then confine that model to some extent? What Barbara has put forward is that we should confine the model to medical genetic testing at this point in time.

DR. LLOYD-PURYEAR: But then that means that the behavioral genetics will not get any scrutiny, and those probably deserve higher scrutiny than whether or not you have blue eyes.

DR. LLOYD-PURYEAR: No, no. It's not that they won't get scrutiny, but that we're saying that they

need such a high level of scrutiny that we can't consider them yet, we'll have to consider them later.

MS. BARR: I think that's a mistake.

DR. McCABE: So why don't we then just put in as a criteria for review medical versus non-medical? The position being that if it's non-medical, again, it might come to very high scrutiny.

MS. BARR: Can I suggest that the behavioral issues that Barbara is trying to address are also embedded in stigmatization. So that we are going to hopefully get there too, because I'm really uncomfortable with medical versus non-medical. Is behavioral medical or non-medical? We've medicalized behavior in our culture.

DR. LEWIS: I like to use the term "health related," because it seems to me that health related is broader than medical, but it gets out of the criminal stuff. So if we were to look at something called health related, that might include some of the behavioral stuff that has some effect on health.

DR. McCABE: Reed?

DR. TUCKSON: I would be comfortable as I listen to the discussion for making – I think there does need to be a distinction in terms of review between medical and non-medical. But I would urge that at least there be some explanatory comment that would suggest, that would be clear that we are concerned about these issues, while we certainly could not tackle everything. But I would not want to leave it unspoken that there are issues that are of enormous social importance that trouble us greatly, but that, in fact, it is not our purview to do it and it has to be looked at in some way, even if we're not able to be prescriptive about it.

DR. McCABE: One of the things, again, that has not been on the table so far is forensics, for example. Again, we can't put our arms around everything. Do you want to say health relatedness, which then probably isn't a word, but that hasn't stopped us before.

So can we get rid of medical versus non-medical and put up there health relatedness? Which again becomes a criteria that is a subject of criteria for the panel to consider.

Victor?

DR. PENCHASZADEH: Just a comment about the potential for stigmatization. We talked about issues of stigmatization of individuals or stigmatization about population groups, and I think that stigmatization probably could be reflected in the wording. We could say of individuals and/or populations because --.

DR. McCABE: So Victor is modifying potential for stigmatization to say potential for stigmatization of individuals and/or populations.

DR. LEWIS: Or. Just or.

DR. McCABE: It's both, I think. It could be both.

Pat?

DR. CHARACHE: This is a new criteria. The concept of the test that has a single developer, versus the format that was described earlier by Elliott. Hundreds of tests and hundreds of labs look at a single entity, and nobody is there to question it. Whereas if you have three or four different university labs or groups doing it, you have a little more interaction and oversight than a single focused individual.

DR. McCABE: So do we want to talk about common diseases versus orphan diseases? It's not quite what you're getting at, but it's a piece of what you're getting at, and certainly we heard in the public commentary quite a bit of discussion about orphan diseases. So we probably need to capture that.

DR. CHARACHE: No. I'm actually just talking about a single developer, because we have some very high gene frequency tests that no one else has looked at before it goes out there.

DR. McCABE: Can you give us some examples?

DR. CHARACHE: Well, some of the colon cancer work which is now scattered to a whole bunch of labs, only one really developed it and put it out there, the familial adenoma polyposis issue which got certain groups into trouble, and nobody had looked at their data before it went out. So it's both commercial labs and university settings, but it's a question of how many people or how much oversight has there been in the course of setting up the test.

DR. McCABE: I'm just trying to figure a way to capture that. Peer review?

DR. CHARACHE: Yes, peer review.

DR. McCABE: Peer review development? Peer review during development?

DR. CHARACHE: Yes, and the peer review could even be done by a consortium group or some other group.

DR. McCABE: But what you were really saying was that if one lab has developed it, then there hasn't been peer review during the development.

DR. CHARACHE: Right.

DR. McCABE: So then a criteria for review would be peer review during the development process? I'm not comfortable -- I'm not really sure --

DR. COLLINS: Haven't we slipped away from criteria into the process itself? This seems like a different concept.

DR. McCABE: No, but what Pat is saying is a criteria for review would be if a single lab developed it so that there had not been multiple labs -- there's the issue of --

DR. LEWIS: The issue of individual versus multiple sites of development. Does that cover it?

DR. McCABE: I'm hearing a consensus that this is process, not criteria. Are there other criteria, then, that we want to address? We won't close any of these lists. I mean, they will be fluid through at least the

early part of our deliberations.

MS. BEARDSLEY: What about the availability of confirmation or confirming --

DR. McCABE: Is that process?

MS. BEARDSLEY: No, no. I'm saying if, for the person who is using the results of this test, there are other ways to confirm this test, there is other information out there, you would have a less, perhaps, interest in a high review.

DR. McCABE: So can you capture that in a few words?

PARTICIPANT: Availability of confirmatory tests?

MS. BEARDSLEY: Yes, availability of confirmatory evidence.

DR. McCABE: We have to have really one person speaking because we need to capture this for the record. Also, our writer is here, Kathi Hanna, and she's busily taking notes so that there will be more than just these bullet points that come out in the draft that she will prepare. So it's important that we get these on the record.

Let's go back to that. We need to clarify this.

MS. BEARDSLEY: I was going to say availability of confirmatory medical evidence.

DR. LEWIS: And what I thought I heard Kate saying was whether the test was the sole method of making the diagnosis or that it was one in terms of a number of pieces that came together.

DR. McCABE: Barbara?

DR. KOENIG: What we're trying to say is a gold standard available or not available?

DR. McCABE: That really has to do with parallel -- I'm not sure of the terms.

MS. BARR: Is it dependency? Diagnostic dependency on tests?

DR. McCABE: I'll go back to my roots in newborn screening. It has to do with multiple tiers of testing. So the genetic tests, the mutation analysis may be only one of those tiers. So would that be acceptable as terminology? Additional tiers of testing.

DR. COLLINS: Why don't we just say availability of independent method of confirmation.

DR. McCABE: Okay, good.

Yes, Mary?

MS. DAVIDSON: I just wanted to come back to rare diseases and ask whether they would be included in

a first criteria of frequency.

DR. McCABE: Yes, I think that's what people, the discussion that probably wasn't captured on the tape, was that orphan diseases come under frequency. I think that Mary's point is and what we heard very clearly from the commentary is that orphan diseases, by not coming to review because they're not as high frequency as others, not then be relegated to the trash heap, as it were, and not be allowed out into the market. So that will be something that we need to discuss probably more in process, really, than here.

Elliott?

MR. HILLBACK: Just understand that we'd better be careful on that definition, because cystic fibrosis is defined as an orphan disease under the orphan drug --

DR. McCABE: Which I think is a reason to use the term "frequency" rather than orphan versus non-orphan.

Ann?

MS. BOLDT: I guess in terms of using the term "confirmation," some tests don't have to be confirmed. They're really independent testing methods. So I don't know if we want to use the terminology "confirmation."

DR. COLLINS: How do you mean?

MS. BOLDT: Well, like in clinical tests for NF, you can just make that diagnosis by the clinical evaluation versus doing the gene test. I guess I'm not sure if we have to say "confirmation" versus an independent alternate testing method. I'm hung up on that.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: I don't understand why that's a criteria for review, because criteria for review is telling you to review, and why would that make it --

MS. BARR: Isn't it how much to review?

MS. BOLDT: If you have other ways of testing.

DR. McCABE: Francis?

DR. COLLINS: Yes, I think because if you have an independent method of confirmation, your concern about false-positives is going to be reduced because you have a way of recognizing them. So I think it does, if you're talking about how you're going to review this, having such an independent method provides a certain reassurance that you'd probably factor into deciding how much attention to pay to that particular test. So I think it belongs here.

DR. LLOYD-PURYEAR: So we might remove something from review. Is that what you're saying?

DR. COLLINS: It would affect your decision about the stringency of the review, I think.

DR. McCABE: Wylie?

DR. BURKE: And I think really that's the point, is that, I think, probably we need to say not "criteria for review" but "criteria for stringent review," don't we? I mean, isn't it implicit that we're going to review everything, at least at some level? By what I mean is that every test that goes through has to fill data in according to a template, and that template has to be reviewed. That could be a very simple pro forma process, and it seems to me what we're saying is there are some characteristics, there are some circumstances under which it would never be a simple pro forma process, because there are certain characteristics that make us want to look carefully.

DR. McCABE: I'm going to propose that maybe what we're doing is entering another category, not a category of test but category for discussion. One of the things we talked about a lot yesterday was labeling and what I think you're really getting at, Wylie, is the concept of labeling. So could we move on to that and discuss that a bit?

DR. BURKE: I agree that I think that's what I'm getting at in part, but to some extent we started with what we thought were the steps or defining things in a research category, and we've now gone into some very important categorization issues, but we still haven't said what the process is and, to some extent, I think we have to have an iterative process here in our discussion. That is, we've got a list of characteristics. My guess is we have enough now for discussion and we should now go to what is the process going from research to clinical use, and how, then, do these categories influence the process?

DR. McCABE: Can you page up on that, or just go up a few lines? The issue is, what we did was Francis described for us testing types, which are really this three-dimensional space that things would map into. Are tests going to differ in the process depending on where they map into that space?

I see heads shaking. Does somebody want to say something? Wylie.

DR. BURKE: Well, I think it's very interesting that the testing types are very useful, those categorizations, and I imagine most of us could pick out along the three continuum the kinds of combinations of characteristics that make us worry a lot.

What I find most useful at this point in our discussion is that we would probably want to ask a test provider to declare where the test fits in each of those trajectories. That is, tell us is this test diagnostic or predictive? Is it a highly penetrant trait or a weakly penetrant trait, et cetera? Are there proven interventions?

So what I find really attractive about that is that, in addition to providing data on the analytic validity and an argument for the clinical value of the test, which are the two things we said would be developed during the research phase, we might ask the test maker to then declare what the test type is in these three lines.

DR. McCABE: I'm going to move us ahead. What I take from what Wylie said is that there are diseases that we could identify where the testing would be diagnostic, the disease is highly penetrant, and there's a proven intervention. So could we take that as an example? So if we could now begin examples.

DR. TUCKSON: I'm sorry to do this. Let me just ask you one question. As I understand the track that we are rolling down, we have established that there is this special first step of research questions from the research phase, and we will establish the analytic validity, and so forth and so on. Now do I understand that all of these questions now begin to move us from the -- we're at the stage now of that transition moment from research to clinical application, and that everything here is part of now that second stage called what are the things that must be raised in terms of the test types and the criteria for review that will determine whether or not and how something goes from research to the clinical application? Is that straight there? Great, because we don't have that as you paged up, and I wanted to make sure I was where you were.

DR. McCABE: Hopefully, we've captured that for the document, because I think it's an important transition point.

Victor?

DR. PENCHASZADEH: Just an interjection. I have a concern before we leave the research stage. The question -- and I suppose it goes without saying, but perhaps we should stress it or mention it, the need for IRB research protocols for any of this research, whether it's federally financed or not, and so forth.

DR. McCABE: Okay. So do we want to capture that under the research phase? I think so. The point is another bullet that says IRB review of research, and I think that that was clear. As part of that bullet, I think that's IRB review of research protocols for all genetic tests. That came clear through the commentaries, and if it's done in the private sector -- IRB review of research protocols for all genetic tests of identifiable human subjects.

MS. BEARDSLEY: Does that include informed consent also?

DR. KOENIG: I think that Victor was making one additional point, however, which was regardless of the source of funding. Is that included, then? Can we make that explicit? Though I'd prefer that that be made explicit, regardless of the source of funding for the research.

DR. McCABE: Okay. So we're going to add to that. Let's make that a sub-bullet, regardless of source of funding.

Elliott?

MR. HILLBACK: I think that the caveat that you added, or Sarah helped you add, was important, because in the other model where there are 20 labs going to develop a test, none of them are doing a research protocol in that sense. There are identified mutations. They're getting unidentified samples from other sources. They're getting known positives and known negatives to challenge to develop the analytical capabilities of their lab. But they're not doing research in the sense that we think of it, and therefore there's no IRB responsibility in that situation.

DR. McCABE: Pat Charache?

DR. CHARACHE: I was also going to raise the question of those settings in which there is no IRB, including some of the commercial units that don't have an IRB required.

DR. McCABE: I think that's captured there, that it's regardless of source of funding, it's all genetic tests.

DR. CHARACHE: But there is no IRB in that institution.

DR. McCABE: But there are commercial IRBs. Western, for example.

DR. CHARACHE: So we're going to require an IRB.

DR. McCABE: It's certainly open for discussion now. But what we just said is that we require an IRB.

DR. FEIGAL: One phraseology that may be useful is "good clinical practices," which is defined internationally in the International Harmonization Guidelines, and it includes IRBs, informed consent, the responsibility to maintain records, all under that category, and it points to various regulations.

There may be settings, for example, a research setting, where you may be doing validation work on an assay where you're not going to notify the subjects that they've been tested. An IRB could look at it and say, yes, this is ethical, the information you're obtaining doesn't need to be transmitted to them. That's the kind of thing an IRB would think about. But I think the more general rubric might be good clinical practices.

DR. McCABE: Could we say under here, "according to good clinical practices"? So another sub-bullet. I know that you're saying that that's sort of above the level, but I think in terms of the way most of us think about it, we think of the IRB. So if we captured that as a sub-bullet, "according to good clinical practices," would that be acceptable?

DR. FEIGAL: Yes, that would be fine.

Another just quick point is that --

DR. McCABE: Could you give us the exact wording? Is it "according to good clinical practices"?

DR. FEIGAL: Yes, good clinical practices.

DR. TUCKSON: Would you accept at least an amendment that there still be a specific identified as a sub-bullet to that the issue of informed consent? I think it's too important to lump in.

DR. FEIGAL: Oh, yes. You could certainly put IRBs in and informed consent underneath that. Those are probably the major parts of that. They also identify some of the things you need in specialized situations, like data safety monitoring boards and other kinds of things that are in there.

DR. McCABE: But now we will add another sub-bullet, "with informed consent." That to some extent, we have to recognize that IRBs may exempt a protocol if they find that it's exceptionally low risk. But if we put in "with informed consent," we've put the IRB in there so that the IRB can elect to exempt the protocol, and there are very specific regulations.

DR. FEIGAL: The other quick comment is the things that Elliott described which are not being researched are still, under the law, investigational if it's not a clear device and requires all of the usual

kinds of considerations, although many diagnostic tests don't require this level of scrutiny. But that's sort of one of the blurred distinctions, is sort of what kind of level of work is being done in an investigational phase.

MR. HILLBACK: GLP ‘s still got to be followed. I mean, good practices still have to be followed. I totally agree with you. I don’t disagree.

DR. McCABE: I'm going to go back to informed consent. What if we say "with informed consent, exceptions being IRB-approved waiver or exemption"? Is that okay to have that in there? Okay.

Okay, anything else? That was important to get that in here.

I think that the next thing that we could do is to begin to look at some examples and so what I'm going to do is suggest that we take a break now. Is it possible to print this out so that we could have this as guidance for all of us as we go on to begin to look at the examples? Do we have a printer here? We do? Okay.

We're going to take a 15-minute break. We will resume at 10:35. There are refreshments in the green room for the panel, and we will have then at everybody's place what we've talked about so far, and we can begin to think about the easy ones first, and we will progress to the more difficult ones.

(Recess.)

DR. McCABE: Let me tell you what I think is the process. I really want to get us concrete and out of the ether, because I think it's important for us to, as we get concrete, I think we will be a little more concrete when we get back to the questions and some of the structure, recognize what we have not dealt with. We have not dealt with the review group on this. We will get back to that today, because we need to settle on who that should be. There may be other thoughts like that that come up and you need to bring those to our attention so that we don't leave stuff out. But I think we will get back to the questions, and that will make sure we don't leave things out.

If we start losing the quorum, and it looks like that's going to happen sometime around 4:35 -- what is a quorum, Sarah?

MS. CARR: It's seven.

DR. McCABE: Seven?

DR. LLOYD-PURYEAR: And that doesn't include us.

DR. McCABE: Right, right. So actually, according to this, as long as no one takes a break between 4:30 and 5:30, we'll be okay. But we're right on it, so we ought to try to end between 4:30 and 5:00 just to be safe. So that gives us the timeframe. Again, we will have what it takes to develop this draft by the end of today.

Muin, you wanted to say something.

DR. KHOURY: Just something that I forgot to mention this morning, because we spent quite a bit of time talking about the U.S. Preventive Services Task Force, and I would like to just give you another example of a similar process that's also a public/private type of process.

The Advisory Committee on Immunization Practices is a body that has academia, government, and industry and consumers that decides and meets on a regular basis, decides on the appropriateness of immunization regimens, should kids under the age of 1 have measles vaccine or hepatitis, this and that. So there are existing examples that are topic-specific, like immunization, where a review process can occur, and it becomes standards and guidelines, and then people go about implementing them. That's just another example similar to the U.S. Preventive Services Task Force.

DR. McCABE: And does that one include federal agencies as well as other organizations?

DR. KHOURY: Yes, right.

DR. FEIGAL: However, it's one where you only review vaccines that haven't already been approved.

DR. KHOURY: Right. That comes to the process of step-wise. Thank you.

DR. McCABE: I think what we're doing is looking at a variety of models, and it's going to be a new model, but it's good to see what has been done before and what works.

Okay, with that, now we're printing out? Where are we on the printing? Do you know?

Let's, can we go back to the three axes? What we're going to do is pick the easiest and the most difficult, and we're going to do the easiest first and then the most difficult later. So the two extremes in this space, if we can agree on what those extremes are.

The easiest, I think that one is fairly easy to agree on. That's diagnostic for a highly penetrant disease with a proven intervention. So could we do that as an example? Diagnostic test for highly penetrant disease with a proven intervention.

DR. LEWIS: PKU.

DR. McCABE: Yes, then we're going to talk about some examples.

Let's start a whole new category below all this, because this is sort of general background stuff. Can we just start examples? No, no. Start another page or something. Just go to a new page. So this will be diagnostic test, highly penetrant, intervention available. Okay? Everybody agrees that that's the easy one. Do you want to go back up to that? We can do the hard one, too. That would be predictive, weakly penetrant, no intervention, no proven intervention.

MS. CARR: Is it no proven or --

DR. McCABE: I can't remember. No proven intervention.

MS. CARR: What if there's not an intervention?

DR. COLLINS: I think it will be interesting to see whether we agree around the table whether the high penetrance or the low penetrance is more scary in this situation.

DR. McCABE: That's why I was saying that I wanted to put this out there so we could be thinking about it as we're doing the easy ones. So what do you want to pick as the most scary? To quote Francis. Do you want to do moderately penetrant?

DR. COLLINS: I think you've got to just pick one, and I like your choice. That's APOe4, isn't it?

DR. McCABE: Okay. So the first, then, is PKU, to give a concrete example. The second one Francis said would be APOe4. PKU being something I spent my entire career on, I like that one. The difficulty with that one is the many mutations. Is there one that we can come up with that's a better PKU example?

DR. LLOYD-PURYEAR: Sickle cell.

MR. HILLBACK: Can I ask on these, was it always this way? Was our level of knowledge when these tests were first done the same as it is now?

DR. McCABE: No.

MR. HILLBACK: So we're taking a current situation and saying this is a test that's been done for 20 years.

DR. McCABE: Right. We're talking about what would a panel that was looking at it now determine, not what they would have determined.

So let's use sickle cell anemia, because I really like that one better than PKU as being a little more absolute. PKU, unfortunately, given our current technology, isn't a real-world example.

So having set those examples, now let's begin to look at the transition. What we're really talking about is the transition from research to clinical practice and how that process would occur, and let's do the one first, and then we'll go to the other.

So why don't we go back up to the examples? I'm sorry. Why don't we start separating the examples, and we'll start inserting information under that category, the easy one.

So what is the process? If we were the deliberative group, we haven't determined who would be the deliberative group yet, but if we were involved in those deliberations, how would we transition from research to clinical?

Pat?

DR. CHARACHE: We'd begin by defining what the information the laboratory that wanted to offer this test would have to possess for review, and this would include the analytical validity.

DR. McCABE: Okay, let's start capturing these. So information required for this transition, another sub-sub-bullet. Information required, and that would include a review of the analytic validity.

DR. CHARACHE: Right, and since it's a diagnostic test, the sensitivity and specificity of the test.

DR. McCABE: Okay. Analytic validity, sensitivity and specificity. Let's get those captured first.

Any other things in that string? David, is that what you were going to add to the string?

DR. FEIGAL: We're still talking about transition from research to clinical. Usually, what's happening at that time is that the diagnostic has settled down and it's a specific procedure. It's not something that's still being changed. It's a point that Elliott discussed earlier as one of the problems in this area. What is it? What's the thing? It's not just the gene. So if they're constantly changing their methodology, slightly changing their reagents, their source reagents, their specific procedures.

So what it means at this time is that you've got a test methodology that's stable, that's worked out by the time you've gone from research to clinical. I can't think of a quick way of summarizing that.

MR. HILLBACK: Isn't that implicit in the analytic validity piece?

DR. FEIGAL: Not necessarily. A lot of that may really be driven by the gene, and you may have different ways of testing that, and you may totally throw out a methodology. I mean, you may want to buy a new analyzer or do something like that. If you think of the way we think about a device, a device is something, and you can't just keep changing it and say, well, just because it gave us the same results, it's still the same thing.

DR. McCABE: But I think what we're talking about is a test. So this isn't the analytic validity of the gene. It's the analytic validity of the test for that gene.

MS. BEARDSLEY: But you have to know what the test is in order to know whether it's analytically valid. So you have to have defined what it is.

DR. McCABE: Pat?

DR. CHARACHE: Perhaps we can say the analytical validity of a stable test.

DR. FEIGAL: Or characterized test method.

DR. CHARACHE: Characterized test method.

DR. FEIGAL: Well-characterized test method.

DR. McCABE: So analytical validity of a well-characterized method.

DR. CHARACHE: Continuing on that string, sensitivity and specificity in the defined target population.

DR. McCABE: So in the defined target population.

DR. CHARACHE: I would add, then, information on the comparative --

DR. McCABE: Before we go on with that, Pat, did you want to comment on this?

MS. BARR: No. Since she's doing other criteria, I'll wait.

DR. McCABE: Okay. Go ahead, Pat.

DR. CHARACHE: The comparison of the proposed test with other diagnostic modalities for the same entity.

DR. McCABE: Can you clarify that?

DR. CHARACHE: If we're adding a genetic test for the sickle cell gene, I want to know how that compares in patient population with sickling under low oxygen situations.

DR. McCABE: So why don't we capture that as comparison with "gold standard," because that's what you're really talking about.

DR. CHARACHE: Test gold standard, as opposed to clinical.

DR. McCABE: Yes, with analytical gold standard.

Yes, Michele?

DR. LLOYD-PURYEAR: In terms of best clinical practices, that should be done. But why would that be a criteria? Before anybody would want to use it, they probably would want to know that. But that should not necessarily be the laboratory's responsibility to show that.

DR. CHARACHE: I think you have to be able to know how to use the new test compared to the test that you've been using.

DR. McCABE: Let's just rephrase that. Let's put the quotes right up against the gold and change test to analytical. But I think Pat's point is that the laboratory ought to be able to compare to a laboratory gold standard. That's not necessarily dealing with the clinical, and we'll get to that. That's your point, Michele, that you really don't know what this is doing in the real world, but we're still in the laboratory at this point in time.

MS. BEARDSLEY: Can I go back to the way we've written this? We're really talking about what information ought to be required to go from research to clinical, right? We're not necessarily talking about the review. Can we delete the words "review of," because we're talking about "the information required includes"?

DR. McCABE: Well, except that there is going to be a group that will review, one or more groups that will review this information.

MR. HILLBACK: Maybe it's the lab.

MS. BEARDSLEY: But does that mean you don't have to get there?

DR. McCABE: I think Elliott's point was really what I was realizing. This is really the laboratory criteria for review, and that will clarify it.

MR. HILLBACK: And we may or may not agree that we want to have some other outside body review this pre-launch, or, as is now the case, the potential is to review it post-launch through the next time you're audited by CLIA. We haven't defined that process yet. All we're saying is there are certain things one has to do. There's quite a long list. This is a major subset.

DR. McCABE: So can we modify this to say, then, laboratory information required?

DR. LEWIS: Can I just try to sort out why we're putting this information under a specific example? Because when we get to the next example, we're probably going to be looking at the same information. I want to know what are the things that differentiate the easy case from the hard case, and this is the kind of information we're going to be reviewing I would think on everything. But what is it that makes this one the no-brainer versus the other one, the one that requires higher scrutiny, if that's where we're going?

This is data. I mean, to me, it would be what the data say rather than the data we're reviewing.

DR. McCABE: Okay, but we're going to need to do for this transition -- the first was research.

Can everybody turn off their mikes, please?

What we first said was that those were research. Now we're talking about the transition from research to clinical, and we can always do a block duplication of this under the next one. But we've got to distinguish some of these characteristics.

Pat Barr?

MS. BARR: I guess the part that I'm confused about, or maybe it's the next block, that after this block there will be another one. If this is what the laboratory is supposed to do and will present, it seems to me that what the group will do is to say, "Did you do your research under the current best practices? Is the material you're presenting to us well presented? Does it do what we would expect it to do?" I think that's where, for different categories, the questions that might be asked by that group would be different.

DR. McCABE: Right, and we will get to those.

Judy, you had something else to say?

DR. LEWIS: I would just see these data as being up above when we're talking about transition from research to practice, and not necessarily under each case, because I think the data that we're going to be collecting would be the same. And what I'm trying to figure out is what's differentiating the easy case from the hard case. I can't see how these data are going to be any different for the other case, so I'm just saying that --

DR. McCABE: Well, if people agree, we can move this up top.

Ann?

DR. KHOURY: Well, just one of the variations is ethnic variations. We could ask that question. Here we are talking about, I mean, sickle cell anemia is the same mutation no matter what population, so I guess that makes it easy. I don't know if we can word that differently, but that's one example that would be different. That would make it higher scrutiny versus less scrutiny.

DR. McCABE: Dave?

DR. FEIGAL: The other thing I would add to the list is, as you go to clinical research, you need to have the clinical information about the test that allows the medical consumer and the lay consumer to interpret the results of the test, whether that's genetic counseling, whether that's informed consent in clinical use. Whatever that may be.

DR. McCABE: That was going to be the next bullet, because this is laboratory information.

DR. CHARACHE: May I comment on that? The laboratory has to have that information before they offer the test. They have to know what information is necessary to interpret the results, and they also have to decide what information they're going to provide as the result interpretation.

DR. McCABE: Joann?

DR. BOUGHMAN: I think it might clarify it if we refer to this as the information required of the sponsor, and that would include laboratory information, phenotype, genotype, or lab result, clinical correlations and several things under that, and then the bigger context that Dr. Feigal just recommended.

DR. McCABE: Okay. So transition from research to clinical: information required from the sponsor.

DR. BOUGHMAN: Or applicant.

DR. McCABE: What's the proper term here? Applicant? Sponsor?

DR. CHARACHE: The developer is good.

DR. McCABE: Okay, developer.

DR. CHARACHE: But I would add those two other components, the information required to interpret the test, clinical information required to interpret the test --

DR. McCABE: Okay, let's do another bullet, then, under that one.

DR. CHARACHE: But that is the laboratory's responsibility under CLIA, and I don't think we should subtract that.

DR. McCABE: What we're saying is that this is information required.

DR. CHARACHE: Good.

DR. McCABE: So clinical information includes -- and what did you say, Pat?

DR. CHARACHE: Required to interpret the test result.

DR. McCABE: So clinical information includes --

DR. CHARACHE: I would just simply say clinical information required to determine if the test should be performed and interpret its results.

MS. BARR: This concept provides that, too.

DR. McCABE: Okay. So clinical information required to interpret the test and to determine if the test should be performed.

DR. PENCHASZADEH: Is that not clinical validity?

DR. McCABE: Wylie?

DR. BURKE: Obviously, that's a crucial point, but even before that I would be inclined to make it as an earlier bullet that the test developer is required to provide information documenting the level of known clinical validity, something along those lines. In other words, there are two separate things that the developer has to provide in clinical information. One is what is known about clinical validity, and basically therefore the justification for using the test, and then secondarily the clinical information that would be required to interpret the test. In other words, clinical validity may be under the condition of certain known clinical information.

DR. McCABE: So something different in this bullet from clinical validity.

DR. BURKE: Yes.

DR. McCABE: Okay. So then we need another bullet. You want it above or below?

DR. BURKE: I think it comes first.

DR. McCABE: After the laboratory.

DR. BURKE: After laboratory.

DR. McCABE: Okay. And you would say just clinical validity?

DR. BURKE: Well, I guess I would say information documenting level of known clinical validity, or information documenting what is known about clinical validity.

DR. McCABE: Can you get that on the screen?

MR. HILLBACK: So, Wylie, is that --

DR. McCABE: Wait a minute. I want to get this, and then we'll move on.

DR. BURKE: In fact, Muin just suggested that maybe it should be what is known about clinical validity and clinical utility. I wouldn't have any objection to that.

DR. McCABE: So clinical validity and clinical utility.

Pat Charache?

DR. CHARACHE: I was kind of including that under the other bullet, which is to define the information to be provided in results interpretation. They are linked, and you can link it either way. You can say information documenting what is known about clinical validity and clinical utility, and information to be provided as results reporting.

DR. BURKE: Yes, that's fine with me. I think it's important to separate them, because there really is a sort of first step where the developer has to say it's part of the rationale for testing, here is what we know about analytic validity, here is what we know about clinical validity and perhaps clinical utility.

DR. CHARACHE: I would like, though, to have -- it can be a separate bullet or it can be an "and" on yours -- the concept that before you transition the test, you have to decide exactly what information you will provide, what sequences you've analyzed, for example.

DR. BURKE: I agree, and I think there might be an advantage to putting it after your third bullet, because we're really talking about sequential reasoning which says we have a valid test, we know what this test means clinically, we have some concept, we know what information we need to have to interpret the test results, and we know what information, basically caveats and limitations, we need to provide when giving the test result. I think that's a logical sequence.

DR. CHARACHE: I agree with that.

DR. McCABE: So can you capture that as a fourth bullet for us, Wylie?

DR. BURKE: I think the fourth bullet, maybe your wording should be put in here, Pat: clinical information to be provided? I'm not quite sure.

DR. McCABE: Why don’t you give us the wording, Pat?

DR. CHARACHE: What I had just scribbled out was information required as part of results reporting, including what analyte has been tested, what allele.

DR. McCABE: Results reporting. There's not an "of" there. Take out the "of" after results, please.

DR. CHARACHE: Part of the information returned to the clinician?

DR. McCABE: Results reporting.

DR. PENCHASZADEH: I'm kind of confused here, because does this pertain to the discussion we had earlier, that without some required information, the lab would not actually perform the test? So we're talking about performing a test, not simply reporting it.

DR. CHARACHE: Yes. The bullet ahead talks about performing the test. This says what the result that's the information returned to the clinician or the consultant must include.

DR. McCABE: It's, again, one of the things that differentiates the genetic testing from a lot of other testing, that there's an interpretation.

DR. PENCHASZADEH: A follow-up thing. I think that the bullet before the last one is still kind of confusing because it may be subject to interpretation as to whether you're saying the test should be approved. You really want to say the test should be performed in an individual case.

DR. CHARACHE: Right.

DR. PENCHASZADEH: Now, shouldn't that be more explicit there?

DR. BURKE: So, Victor, you're saying that the third bullet should say clinical information required to interpret the test in an individual case, to determine the test, and to determine if the test should be performed in an individual case.

DR. CHARACHE: Right.

DR. McCABE: So at the end of that third bullet, we'll just insert "in an individual case."

Muin?

DR. KHOURY: I'm having trouble separating the initial review, the process of review, from the implementation of actual genetic testing. I mean, the kind of data we need initially for a quick review are analytic validity, clinical validity, and clinical utility. Then, once there is some initial blessing, then the implementation of testing in particular labs will require the CLIA stuff in terms of pre, post, and analytic. I don't know how much you need to get into that at this level of review.

DR. McCABE: Wylie?

DR. BURKE: I actually think I'm following Pat's reasoning correctly, that you actually need to disclose this because you're actually defining limitations of your knowledge about clinical validity. In other words, understanding what you know about clinical validity or defining clinical validity for a certain test use often requires clinical information to be available when the test is taken and clinical information to be provided as part of the test delivery. It might be that there will be tests where there is no clinical information, it's so straightforward. In other words, if those boxes don't need to be filled, that's fine.

DR. McCABE: Muin?

DR. KHOURY: I guess what I'm saying is that clinical validity is not just a 2x2 table. It can be stratified by age and population group and all of these things. So as part of the review of the analytic and clinical validity and clinical utility, you need those things anyway. It's part of the package.

DR. McCABE: Okay.

DR. CHARACHE: One modification. On that last bullet that says "clinical information required as part of results reporting," it is also the laboratory information as well. So it's really information required. We can just remove the word "clinical."

DR. McCABE: Why don't we just say "clinical and laboratory" or "laboratory and clinical." Why don't we say "laboratory and clinical."

Yes, Elliott, and then Kate.

MR. HILLBACK: Could I just ask some of the geneticists here what percent of the time this information is going to be actually represented by citing papers, peer-reviewed papers that have been done by the researchers who have been studying the disease, rather than new data generated by the lab?

DR. McCABE: I think that's up to the panel to determine whether they would accept that.

MR. HILLBACK: In the real world, in the real world today.

DR. McCABE: Well, certainly if it was an example where there were a lot of data in the literature, and we picked one where there is, then one could cite the literature.

MR. HILLBACK: But even if there's only one or two papers in the literature but that is the body of knowledge, most laboratories don't go out and recruit new patients to do the downstream analysis that's mentioned here. So the data that's available, whether it's on BRCA1 or APOe4 or our simple example here, it's the data that's in the field. It isn't the lab's. This is where you get 10 labs saying we'll do this at the same time. They're not running 10 clinical trials. They are all citing probably the same papers, although in the BRCA1 case, where Pat and I were on the other task force at that time, it became clear that different labs were citing different papers. So they were citing actually different levels of penetrance, different alterations or risk factors.

DR. McCABE: But that's part of the purpose of having a review group rather than this being done on an ad hoc basis in each laboratory.

Kate, then Pat Barr.

MS. BEARDSLEY: I was going to propose one more bullet here. This may seem obvious, but you also need to move into clinical use, some statement of what you're going to say about the test. In other words, the translation of everything here into a statement which probably at some point turns into promotion of some sort. So it seems to me that you have to have that written down.

DR. McCABE: So how would you capture that?

MS. BEARDSLEY: Well, I think classically you would say labeling. It's labeling. It's a description of the test that you've gleaned from everything else.

DR. McCABE: So another bullet, description of the test -- i.e., labeling.

DR. PENCHASZADEH: You mean for the public?

MS. BEARDSLEY: Right. For whomever needs to know.

DR. McCABE: Pat Barr?

MS. BARR: I see no problem with the lab or sponsor relying on printed published papers. What I would like to add to that is that there be a search of published and unpublished, because there's always a bias in terms of what gets published, and in a real analysis, if you can get at that other material -- I don't know how easy it is to get at that at all -- it would be helpful.

DR. McCABE: I'm not an expert on this, but my understanding is that the provision of proprietary information is voluntary. But maybe that isn't the case in other examples, Dave.

DR. FEIGAL: Well, the sponsor usually has to disclose everything they know, but then there's stuff that may be proprietary in their competitors' files that they wouldn't have access to and we don't have the authority to share with them.

MS. BARR: I was really asking about the process Cochrane uses when they're trying to gather data.

DR. KHOURY: I agree with Pat. I think part of the experiment we're currently doing with hemochromatosis and CF as examples for these kinds of data collections is to evaluate both published and unpublished literature. When I say unpublished, some of it could be published. In other words, there could be a paper by a group that publishes results in a certain way, they present some aspects of the data. But when some group decides that this is the data we want, then they go back to the people and say, well, give us the additional data that you didn't publish from the same study, and that makes the comparability of Study A with Study B with Study C.

I mean, these are principles of meta-analysis that can be applied.

DR. McCABE: So can we put another bullet that information should include published as well as unpublished information, to the extent possible? Thank you.

Elliott?

MR. HILLBACK: I'm just a little concerned that we talk as though it's a fait accompli that every time a new lab wants to do a new test, we're going to go to some panel. I don't think we've made that recommendation yet, and so I don't think we should talk about always having to go to an outside party. I think what we've tried to talk about previously is develop a process that has the hoops in it that have to be jumped through in order to go to the market, in order to go into clinical practice. Let me say it the right way. And I think it's important to remember that there may be lots of times where setting up that series of hoops and then monitoring from the side is what’s going to be the best for this care.

And we shouldn't assume that one of the hoops is to go sit in a queue and wait for someone to look at this. I think that's a presupposition that I don't accept yet. Maybe some people have come to that conclusion. I haven't, and I don't think as a group we've debated that yet.

DR. McCABE: I think that will come out as we get back to the questions. I really want to try to stick to the examples and not get too fuzzy, or I'm afraid we're not going to get anywhere.

Wylie?

DR. BURKE: Just a quick comment on that. Elliott, I think it's completely compatible with the consensus we're developing here to say that this kind of process needs to occur the first time a test comes into use, and we can discuss it later. I think it's really a minor point that if a test is already in use and a lab that hasn't done the test wants to now start doing the test, that as long as that lab can establish that it's following the same methodology and principles that have already been approved, it should have a quicker review process.

I think those are separate issues, and I certainly don't think that we're talking about a process that would have to be repeated redundantly every time a new lab decided to do a test.

DR. McCABE: We'll come back to this discussion. I don't want to get side-tracked.

So what we have done is we've established, then, these as sort of general criteria, and probably as other people think about it, you'll think of other ones. But it gives us an outline. Remember, we're going to have two months that this draft will be reviewed by others, as well as by ourselves.

But let's get back to Judy's issue or someone's issue that we really need to go through the process now. What do we need for sickle cell disease? What is easy or hard about sickle cell disease? So can we just go back up to the top of this and see what we had? So this was a transition from research to clinical information required. How would you capture your thoughts, Judy?

DR. LEWIS: Well, my question was that I thought these were categories that came up above the two examples, and that this was data that we were going to be looking at, and that then we would look at each example. So I thought that this laboratory data and this clinical data came above the example in our outline rather than below, and that then we would look at applying all of those things, because I didn't see how those particular criteria differed from one example to another. I mean, the data will, but the categories won't.

DR. McCABE: Pat?

MS. BARR: It would seem to me that the difference is that we might be able to all agree that sickle cell, if presented with what we know now, would clearly be some kind of expedited review, almost a check off and you're on your way; whereas we get to CF in the early stages, not quite as expedited a review, but it might be for the population they want to do it in because of the good literature, step 2 of the expedited review.

So I think the question that Elliott is struggling with is that he says let us do it, and let CLIA come in and check that we've done it. There are others of us around the table that are thinking is there some way we could have an independent group look at it before you start marketing it out there or providing it out there as a service? That should be pretty efficient and quick, but it's an independent review rather than a lab-sponsored review.

DR. McCABE: To try and capture some of this for this example -- and again, I want to try to stick with the example -- we have this bullet "transition from research to clinical." Do we want another bullet for a well-established test with substantial literature and experience, one should have expedited review?

Pat?

DR. CHARACHE: I'm going along I think with Judy's thought, that all these criteria still have to be in place, that the difference is the review process.

DR. McCABE: What we can do, if you wish, is that we can now move this in a block and say that this is required for all tests, this bullet and all the sub-bullets under it are required for all tests.

MS. BEARDSLEY: Can I just see if this strikes anybody else? We've talked about what you'd like to have to take a test from research to clinical. We haven't talked about the standard, how you know when you're there. I mean, you could have a test where you have analytical validity and it's lousy, and you have clinical validity and it's lousy, and what we haven't talked about is how to apply this to know how much is enough. That seems to me to be a different question than the question of review, because if you had a standard that says this much is enough, and it was a really good standard, and you could make it work, then you'd have less need for review. But if you have no standard, then you have to have lots of review.

DR. McCABE: Wylie, then Pat.

DR. BURKE: I agree completely. I think that's a crucial point, and I think that's where our other testing criteria come in, because I think what is implicit in our conversation is that what's enough is going to be different according to certain criteria. That is, for certain kinds of tests, you've got to have more before you're ready to go forward. What I'm really uncertain about is whether the standard differs by our second list -- that is, our list of criteria -- or whether it also differs by diagnostic versus predictive, et cetera. I'm not sure it does, because I think the first list may just be describing the kind of data you're likely to have.

DR. McCABE: Pat, Reed, and then Elliott.

DR. CHARACHE: I also agree that there should be definitions of each of these factors, and I have suggested a couple of times, therefore, that there be a template developed which defines what you need to know about these things. Also, as part of the review process or any other way we want to do it, I think this can be defined differently for different genetic tests, the example being low prevalence versus high prevalence tests, and therefore how many kindreds you need.

DR. McCABE: Reed?

DR. TUCKSON: I just want to make sure before we leave the list of issues, help me to understand. For sickle cell disease, while it is one of our easy ones to do, the issues of the stigmatization and the implications for a subpopulation of Americans -- I lived this issue intensely. Is that part of the data set that needs to be at this level, or is that a consideration that occurs at the level of the next step we get to, which is wherever that review is? Because if Elliott's point holds the day, then it could be the laboratory or someone who would make some judgment about those issues versus some other body. So I'm a little confused on this point.

DR. McCABE: I think certainly that is an important issue, and that's going to differ from test to test. It had to do with our general criteria above regarding stigmatization of individuals and groups. But certainly, it's going to need to be applied to every test. It's one of the things that would not be specific to this example. It needs to be considered broadly, but one could look at it specifically within --

DR. TUCKSON: Does that mean that we collect -- should one of our data points be the collection of information relevant to those things? I thought that's why we put it up there. So I'm just trying to make sure we add that as part of the equation in some way, or is that not to be a part of the equation?

DR. McCABE: Again, that would be true for all tests, so one would need to put it as a bullet to certainly consider. So let's go to the bottom of these bullets and see where it fits in.

Wylie?

DR. BURKE: I think we should go up and look at that list, the list that started with prevalence, and ask whether every one of them should be handled the way that Reed just mentioned. I mean, do they all represent characteristics that the developer should define for their test?

DR. McCABE: I'm sorry. Go back to which list?

DR. BURKE: The criteria for review.

DR. McCABE: Okay. You all have in front of you the criteria for review, which we said was frequency, population-based screening versus individual testing, potential for stigmatization of individuals and/or populations, health relatedness, availability of independent methods of confirmation. I think that all of these really belong there, and again, it fits in with a block that could be all tests.

Judy?

DR. LEWIS: I'm not sure I'm going to say this the right way, but I think there's a difference between testing for diseases that occur exclusively or predominantly in one segment of a population, the example being something like Tay Sachs or sickle cell, where pretty much you're only going to be a candidate for testing if you're a member of that subpopulation; versus something like cystic fibrosis, where the test means different things for different populations in that cystic fibrosis may occur in all these populations, but the tests we've got are only relevant because they only give good information to different populations.

I think those are two very different issues, and I think that the way we deal with them has to be sensitive to the fact that one of them is what your genetic characteristics are, and the other is that we don't have a test to help you. I think those are two very different issues, and I'm not sure I'm expressing it the way I need to. Wylie is shaking her head, so I think maybe I am.

DR. McCABE: Where should that go?

DR. LEWIS: I just think that's a piece of the stigmatization piece in that if we're careful, I don't think diseases that occur in one subset of the population and others is necessarily stigmatizing. I think the piece that becomes a problem is the discrimination in terms of -- there's a difference between discrimination and stigmatization in terms of the testing and if we don't have a good test, but yet we have a consensus panel that says everybody should be offered cystic fibrosis testing, and then we have a subpopulation that gets very concerned because we're saying you should be tested for something that's not relevant but you're not paying attention to diseases that are relevant for our population, that's different at some level.

DR. McCABE: Muin, and then Victor.

DR. KHOURY: I think we're getting a bit bogged down.

DR. McCABE: Wait a minute, I think I skipped over Elliott.

MR. HILLBACK: By picking this easy situation, I'm sure that neither sickle cell or PKU started off in this position, and I think we're deluding ourselves to think that we start at a point where all this data is available and we have this situation where we know so much about a disease, and now we're going to launch. There are very few situations like that. There may be a few more, but I think it's that issue.

Again, I guess the other question is for someone who is trying to take a test from research or from the development phase into the clinical phase, I don't know how an individual developer needs to, other than making sure that the information they provide is as accurate as possible, how does an individual developer of a test, maybe 20 different labs all doing it at the same time, how do they get involved in these social issues? Again, we have to be sensitive to them, but I don't understand how that quite gets in this process.

DR. McCABE: Muin, Victor, Pat Barr, and then Wylie.

DR. KHOURY: I want to agree with Elliott and others. I think we're getting a bit bogged down here, but I was looking at sickle cell from a point of view of data, and I looked at the criteria for review about frequency and then population-based screening versus individual testing. There are newborn screening programs for sickle cell disease, and they do whites and blacks and everyone. Every kid is now tested for newborn screening regardless of ethnic affiliation or otherwise.

I think I'd like us to step back a little bit and take a look at the big picture. There is a new test coming down the market, there has to be some initial review using a template that I think we're trying to construct for the test developers that provides this kind of information. We're going to, for the most part, expedite the review process, unless there are some real snags, like testing only once for sickle cell disease. I'm stepping back maybe 10 years ago where that decision hadn't been made, for example, and there was a lot of debate.

But then provide another template for how further data can be collected. So there is an initial review that's quick, that helps out using a specific template that collects the data on analytic and clinical validity and utility, as well as these other kinds of data endpoints. They don't have to be very extensive, and then you launch something, you collect further data, and then you come back, and maybe at that point you do a more extensive review. But if we're going to bog the system down with everything, we're back to square one.

I mean, even the easy one, like sickle cell disease, doesn't look very easy anymore.

DR. McCABE: Victor?

DR. PENCHASZADEH: On the same line, I would admit that what we consider easy today was not easy 10 or 15 years ago. So it may be deceptive to call it that way. In addition, most likely whenever we go to the other category of the most difficult category, we will probably review exactly the same items or information needed that we are considering now for what we are saying is the easiest category. So I'm not so sure that it really will matter that much in terms of the type of information we want for review,

which category we are talking about.

But addressing the earliest concern about how you factor in social issues, I think they have to be factored in. I mean, how is a matter of discussion, but they necessarily are part of what a test means. If it is the type of information that will be needed for any independent review board, where they will say that this is a test that can go to market for clinical application, which means that whoever wants to develop that test will have to, in some way, to have considered all the possible social issues implied in the application of that test. That is subject to review before marketing a test.

DR. BURKE: I actually think that in this discussion we need to be very careful to avoid mixing up the types of information, the categories of information that we want to have on a test versus the threshold we might consider is needed for initial use. If you look at what this conversation led to, whether we should add all these bullets into the initial information, I would argue that we should, possibly phrased a little bit differently.

But let me put it this way: I think when you want to bring a sickle test to market, you should have some information about the prevalence of that test, you should know whether you're proposing it for population-based screening versus individual testing. The potential for stigmatization of individuals and/or populations is translated a little bit differently. You should be able to provide information, what you have, which might be rather limited, about the prevalence in different populations and the likelihood that the test would be targeted to one population or to the population as a whole. That's part of thinking through what you're going to use the test for.

You certainly should be able to provide information about the health relatedness and the availability of independent methods of confirmation, which could be a simple no.

I think the issue really is not that all these categories should be provided. The whole list that we have is not a bar to quick review. The question is what's the threshold you need to achieve? Going back to Kate's comments, I think we have to define that threshold. So we have to say here's the 20 categories of information we want you to address, and here is where you need to be for initial approval.

DR. McCABE: Michele, Elliott, and Pat Charache.

DR. LLOYD-PURYEAR: I agree with that.

DR. McCABE: Elliott?

MR. HILLBACK: I think that's right. I think Wylie's got it right. I think we were in a situation with cystic fibrosis, as an example, where the early versions of the test, even up through 30 and 40 mutations, didn't do a very good job in the African American population at all. As we've gone to 86 mutations, we have directly addressed that to some degree, and also various Latin populations as well. But at the time we launched it, we knew that it wasn't very appropriate for those subpopulations, and that's part of developing the test.

But I think the sensitivity and a lot of feedback we got from a lot of physicians saying we need to address these other populations led us to do that. So I think we have to be sensitive to these issues, don't get me wrong. But I don't know it's a release criteria for a first move into clinical use, but you have to know

what you have and what you don't have.

DR. BURKE: Exactly, and really the implication is for ongoing data collection. The reason why that's a crucial point is, it seems to me as we've heard discussion about this, it's systematizing ongoing data collection that probably is the biggest missing link in our current system.

DR. McCABE: Pat Charache, and then we're going to go back and resolve some of these on the document.

DR. CHARACHE: I would just add to what Wylie has said. These are the components that are used now to assess all tests. With the home brews, it's done by the laboratory, with subsequent CLIA oversight. For the other tests, it's done by the FDA. Where the variation comes in is the stringency that's applied to each of these factors.

DR. McCABE: So listening to this discussion, can we go back down to the examples? At the top of the examples, I think what we really need to do is now take these as -- these should become a major bullet under that other criteria, and now we go back to our examples. I don't know the easiest way. I would just move examples of diagnostic, highly penetrant, and move that down to the second example.

DR. LLOYD-PURYEAR: Wouldn't you require this kind of review on all tests?

DR. McCABE: Yes, that's what we're saying, that for all tests we're going to go back and talk about the examples.

DR. LLOYD-PURYEAR: The point is to define what you think your test is for, and the categorization, therefore, doesn't define the review.

DR. McCABE: Right.

DR. LLOYD-PURYEAR: So the categorizations aren't necessary.

DR. McCABE: What we're going to do is we're going to talk about the categorization defining threshold.

MR. HILLBACK: It doesn't define the content. It may define the threshold or it may define who all looks at it. I think that's more relevant than what information. I think the categories of information are fundamentally the same.

DR. McCABE: Right. So let's go back down to the examples. Do we want to talk about it in terms of threshold? How do we want to deal with this?

Pat Barr.

MS. BARR: I'm just wondering if we shouldn't, since Elliott is here, do CF at the earliest moment that he can remember, where were we, and we can talk about, then, in an ideal world, what would be the best way to get that out but get it reviewed.

DR. McCABE: Okay. I think a larger part of the queue are the ones that are already out there where we

have a lot of experience, sickle cell being the easiest end of the spectrum. So we could add that one if you would like, but I'd like to do sickle cell disease. This would be basically a review of the literature, right? I mean, this exists in the literature. So it would be a documentation of the method and review of the literature for the criteria. So why don't we say, under sickle cell disease, documentation of the method, meaning SOPs, review of the literature regarding answers to our criteria, and the third bullet would be expedited review.

Yes, Pat Barr?

MS. BARR: I'm just a little nervous just because of our experience. Who addresses it and how does the stigmatization issue get addressed?

DR. McCABE: David?

DR. FEIGAL: Well, I think the missing part here is that in cases like this, with preexisting testing programs, you're leveraging off of existing systems. So essentially all the kind of counseling, all the kinds of things that have been done with sickle cell programs in the past, you're just talking about swapping in a new diagnostic method for an old one, but you're not disrupting any of the other kinds of things. So that's the other thing that would be part of sickle cell, is embedding the new methodology in the clinical framework where all of the counseling, the consent, all of those types of issues were taken advantage of.

DR. McCABE: Let's not make it so absolute, then. We can say "option for expedited review."

Barbara?

DR. KOENIG: I'm willing to accept option for expedited review, as long as it's option. But I think also if we're thinking of this as a model for prospective kinds of tests, if we are saying that it's going to be a test targeted to a particular subpopulation, then by definition, if we're taking our categories seriously, then this would have to be one where perhaps -- even if the analytic validity were there, even if all those other things were there, you might want to have a high level of oversight because of the social issues.

DR. McCABE: But recognize that there was a huge problem with stigmatization in the 1970s with sickle cell disease, and then as it's become universally tested for, as we've developed the community-based sickle cell associations, it still has the potential for stigmatization, but my own impression -- but I'm certainly not a population being stigmatized by this -- is that this has become less of a concern within the community today than it was 20 years ago.

Pat?

MS. BARR: But that's precisely the point. I don't think we want to ask a population to go through 30 years of stigmatization and difficulty. So it would seem to me that when you are focusing on a particular population, which might be the population that has schizophrenia, you're going to have to address conditions or some system before you put this out to market that's going to cope with that to try to avoid the kinds of problems we had with sickle cell 30 years ago.

DR. McCABE: I was looking at this as an example of something in the queue where we do have 30 years

experience.

Wylie?

DR. BURKE: I would just add to that that I think this discussion provides some illumination regarding Elliott's point about how much information would a test developer be required to provide. In fact, if we had a category that included targeting to special populations and potential for stigmatization, it would be very much in the interests of the test developer to provide the kind of data we have now on sickle cell testing; that is, how issues of stigmatization and acceptability to tested individuals are being handled, the history of it, why this is now something that we need have less concern about.

So this is an invitation to the developer to provide as much information as would be helpful to the case for proposing the test. If that information is not available, that's part of the disclosure, and it then appropriately bumps it to a more stringent review.

DR. McCABE: Reed, and then Judy.

DR. TUCKSON: Just a very small point on this. I would urge editorially that if we're going to use this as an example, we will talk about the 30-year history, but I would not proclaim that the issues have gone away. That would be presumptuous, I think.

DR. McCABE: Judy?

DR. LEWIS: I think part of what we're doing is focusing on a very small part of the process, which is the laboratory piece, and I think that's a necessary piece, but I don't think it's sufficient. I think the whole issue of oversight deals with far more than the laboratory piece. When you start talking about introduction into clinical practice, part of it is making sure that the test is accurate. The second piece is making sure that the people downstream from the lab are appropriately educated, and that's the consumers and the providers. So I think that the laboratory piece is necessary, but I think if all we do is focus on the laboratory piece that we're creating a disservice.

DR. McCABE: Elliott?

MR. HILLBACK: Can I ask Wylie a question? You talk about raising this to a higher level of review because of the potential for stigmatization. So what decision would you make? You'd make a decision that we won't introduce the test because of that, or you'd make some other laboratory-based review, or you'd say until we can teach all the physicians the social issues that are going to take us a long time to learn anyway -- I don't know what would be different, why you'd want an elevated level of review.

DR. BURKE: Let me give you an example. Suppose we have a new test that we think looks like a sickle cell trait test. It has a number of those characteristics, but it's a test very specific to a couple of Native American groups in this country.

MR. HILLBACK: Finnish Americans.

DR. BURKE: Well, I'm deliberately choosing Native Americans as an already stigmatized group that has concerns about issues of genetic labeling. I think the mere fact that that test was going to be limited to

those populations even though it met other criteria that would normally cause rapid review would require just a pause and thinking about it, and I believe what would happen very quickly would be that whatever board was doing this would say we need some community input here, and it needs to be very specific community input; that is, input from the community that is going to be targeted. That community probably isn't going to have standing input on the board.

If, indeed, the test has the characteristics that we think it has, I think it may be a very rapid process of agreement with the community that this is a good thing and under appropriate circumstances should go forward. But I would say that I think that is exactly what the history of sickle testing tells us we should do.

MR. HILLBACK: Would you do that with new treatments as well, have the potential patients be involved? I don't understand why you start putting in delays or putting in changes to the process. I understand why you would want to make sure that the information can be provided in an appropriate way, and that if this is a disease that isn't known, a condition that isn't well known, that the education about why being a carrier isn't the same as having a disease, for example, is well known in the population. That's part of the counseling process. But I'm not sure you'd change the review process.

DR. BURKE: I'll let Pat respond, but I just want to say quickly that I'm responding in part to what I think has been very vivid public comment on this and what remains a very troubling issue within genetics; that is, the reason why we have potential for stigmatization on our list, and it probably wouldn't be on the list of other kinds of laboratory tests, or at least not as readily, is because this is a big issue in genetics.

DR. McCABE: Pat Barr?

MS. BARR: And it's different than treatment, which tends to be an individual issue and a choice of an individual in a doctor's office, and well-published information about a group carrying a particular mutation which gets interpreted at this moment in time in our society. I think what we talked about was a fluid process. So whereas CF may have been stigmatizing 20 years ago, it is not now. Whereas sickle cell clearly was stigmatizing a number of years ago, it is far less so now. So we have to accept that the scrutiny will change over time. I think that was the basic premise of what we talked about in terms of it being a reiterative process.

So there are populations that are already stigmatized. So when you then target a genetic test to those populations, that community deserves some recognition and appropriate cautions.

DR. McCABE: To get back to the example, I think all this is helpful information, but I think again we're trying to deal with some concrete examples here. We could capture some of what has been said by putting another bullet in and saying that after release, ongoing evaluation of stigmatization and clinical efficacy. No? If, with this example, which is used in newborn screening throughout the country, we're going to grind it to a halt, then we are doing a major disservice I feel -- I'm speaking not as the chair now but as a member of this committee -- then we have done a major disservice to the people of this country.

On this one with 30 years experience, if we can't come to some way of expediting the review but recognizing the ongoing problems, then we aren't going to be able to do anything.

MS. BARR: But why does this come in? It's out there. Are you suggesting that every test that's out

there, we're now going to pull in and review? I thought that what we're in the business of doing is talking about new tests coming out and what's the review that's going to be done.

DR. McCABE: Well, does that mean that every test, is there going to be a flurry of activity over the next two months to release tests? I'm serious. People know how to game the system.

PARTICIPANT: Yes, there is.

DR. McCABE: But then are they all going to be grandparented in, or are we going to do a quick pass at what's out there? I mean, we aren't going to do it, but recommend a quick pass at what's out there to pick out the APOe4s versus the sickle cell disease?

Pat Charache?

DR. CHARACHE: Can we change what has been said here? It's documentation of method, review of literature. Can we add review of literature and social issues?

DR. McCABE: Those are already in the other material.

DR. CHARACHE: Yes, but would that help resolve this?

DR. McCABE: I don't know.

Pat?

MS. BARR: What about prior experience on the market? That would tell us with sickle cell that we're pretty content that we're going in the right direction and those programs stay. And that would allow us to do fast reviews of the stuff that's out there and pull in the stuff that we think is being misappropriately used.

DR. McCABE: So that would be a third bullet before option? What was that again, Pat?

MS. BARR: Experience on the market to date.

MR. HILLBACK: I don't understand what problem we're trying to solve now.

DR. McCABE: I've lost track of the order.

Victor?

DR. PENCHASZADEH: I think that part of the confusion is that we decided to look at sickle cell not necessarily because of the heading there, and not only because of the heading, but because it has already been in the market for years. So perhaps the heading there should state tests that are already in the market, because then a different set of issues may come up with a new test that fits the same criteria there but it's a new test for a new condition.

DR. McCABE: Ann, and then Reed.

MS. BOLDT: I think we need to go back to what Wylie was saying in determining what the thresholds are. I don't know if we want to try to assign a number or something that makes it somewhat objective, that if they meet this certain number after looking at each individual criteria that we were talking about, that that's when you would expedite a review? I think we have to assign some type of system, a number system or something, looking at each individual threshold, and we haven't done that. So we're trying to figure out this without establishing the thresholds.

DR. McCABE: Reed, and then Muin.

DR. TUCKSON: I really think that we chose sickle cell for the reasons that are on the board and not because it is a well-established test. I think the issue of how to deal retrospectively is a separate issue that we ought to come to later, or it will just distract the hell out of us. I do think, though, that where we really are in the real issue that we are now at is the question of whether or not there is going to be some organizational entity that will be responsible for looking at these other considerations, or whether we're going to "burden" the laboratory to be the sole place where these issues are raised and then resolved.

I just think that we are really at the point now to just define what is the difference between what the lab does, what the threshold is for what the lab does, and then what process overlooks all that stuff that doesn't stifle but that allows these more subtle nuances to be addressed. Finally, I would simply say that I do think it's exceedingly important that the lab be responsible for thinking through the questions. Scientists cannot avoid the implications of their research. We've had enough of that in history. On the other hand, they shouldn't be the place where it's all resolved, so there has to be some other mechanism. I think we ought to get to that real quick.

DR. McCABE: Muin, and then Elliott.

DR. KHOURY: I was going to agree completely with Reed here. According to gene tests, there are already 700 or 800 DNA-based tests on the market today. If we're going to go back -- and I suggest we might want to go back at some point and look at these 700 or 800 tests from the point of view of the kinds of data we want that includes both social issues as well as the analytic and clinical stuff -- I think we need to look forward. I mean, 10 years from now there will be 7,000 on the market.

We started here, and I think this is a good starting point, is defining as a framework the kind of data that will have to accompany the introduction or the transition from research to practice. Having decided what those data look like, we can massage them a little bit, but then what happens after that? The ongoing data becomes part of the knowledge base that some group can either submit -- the lab, for example -- or a group can collect it on their own and decide this is the knowledge base of what we know today. Do we cross that threshold, or we don't?

If we do, then next year that same report card on that genetic test will change because there will be additional data. So what's the mechanism to capture the additional information, which includes the social issues? I don't think we can neglect that. I mean, it's not only about analytic and clinical validity. It includes what happens to people who get tested, and that to me is a very important part of it.

DR. McCABE: Elliott?

MR. HILLBACK: I agree with both Reed and Muin. I think where we get to is that the process we're

trying to define is what has to be looked at so that the test can move into medical practice. Once it's in clinical practice, it's used by clinical practitioners who are practicing medicine, who are working with patients, and that's when a lot of these other issues have to be dealt with. They aren't dealt with by the lab. They're dealt with by the medical system. The lab is providing a piece of information to a physician to do something with, and to make the lab the lightning rod for dealing with all these other issues I think is an inappropriate point.

I agree that we have to think it through, we have to understand what the implications are, if there are subgroups where this is more penetrant or where there's a higher occurrence rate than others, but that isn't where we get at the issue. We get at it in the whole practice of medicine, the practice of genetic medicine. I think that's a different issue than is this test a useable test.

DR. McCABE: Pat Barr?

MS. BARR: Elliott, the thing I think you're forgetting, and I think I'm being more protective of you than you are, is if we have a few more bad experiences with particular groups, you're going to get closed out. That's what's going to happen. I mean, what we want to do is move this in a smooth way so that people are comfortable, groups feel protected, and there's accountability, so that we don't get the kind of thing that's happened in the New York Times with gene therapy research.

I mean, I really feel very strongly that we've got new technologies coming out, a tremendous amount of skepticism about this technology, other people telling us it can do a tremendous amount of good, and we need a system that balances those things.

DR. McCABE: Reed?

DR. TUCKSON: First of all, I think Elliott raises an important point. I would also, though, say that, especially from the physician side of this, I really like what you said. But these tests are also being developed as entrepreneurial ventures in a very large number of cases, and given direct-to-consumer advertising and this whole new era in the way in which these sorts of things get marketed, there really is an enormous potential for mischief and harm, not by your fine firm but by some other people out there.

DR. McCABE: I think that maybe we need to delete these examples because they've distracted us, and go back to the process. So why don't we just delete from "Examples" on down. I just thought we were getting back to a process. Get rid of APOe4. Do we want to leave in an option for expedited review or delete that?

MS. BEARDSLEY: I'm confused now. Are we saying that basically all we're going to require is a review of the literature to put a diagnostic highly penetrant intervention available test on the market?

DR. McCABE: If there's a literature that exists.

MS. BEARDSLEY: And what if there is none? Then you can just put it on?

DR. McCABE: No.

DR. BURKE: I think we want answers to the questions. I think we want all of the criteria.

DR. McCABE: Right, but I think what we were saying is that for some diseases, those answers exist in the literature. I mean, it's the issue of trials. You don't have to do a new clinical trial if the data already exist in the literature.

Pat Charache, and then Judy, and then Victor.

DR. CHARACHE: It may be included under "Documentation of Method," but you do have to show that your laboratory repeats the performance that's in the literature, which doesn't take a lot of testing. It just validates your method vis-a-vis the literature.

DR. McCABE: And I thought that was captured in documentation of the method.

DR. CHARACHE: I think it is.

DR. McCABE: Okay.

Judy?

DR. LEWIS: What I was going to suggest is that we add to the examples under diagnostic, highly penetrant, intervention available, test currently in use.

PARTICIPANT: No, no.

DR. LEWIS: What I was going to suggest is –. I mean, this goes back to what Ed was saying, that if we've got data on a test that's currently in use, we're going to be doing something different than something that's coming to the market for the first time. In terms of reviewing what's already out there, we're not going to grandmother or grandfather everything. We're going to review what's out there, but we're going to do it in a way that doesn't take the test off the market while we're reviewing it. We're going to look at the data, and we might have a different thing for something new that's coming down the road that we want to see before it gets put to market rather than something that's already there.

Maybe the experience on the market to date does it. If there is none, then it has a different level of scrutiny.

DR. McCABE: Victor?

DR. PENCHASZADEH: Actually, I think what we are doing when we took that sickle cell name from there is actually talking about new tests. That's what I understand. We decided that we are not going to tackle now the tests that are already on the market, right? So we're talking about new tests. No? Yes, we are. Which means that then, in my view, we have to be a little bit more explicit, because on those four bullets that we outlined there, we were assuming that there was already a test on the market and that there was literature there to be analyzed, so on and so forth, that there was experience in the market.

So what do we need to require for diagnostic tests, highly penetrant, intervention available, on any new test that is put up on the market? I think that what Pat Charache said about the lab being responsible for putting up data for review, if it is a new test, most likely -- well, there may be literature, but there may not be literature. So we should have a bullet there on what information the lab should put forth.

DR. McCABE: The reason why I suggested that we delete both of these examples is that I don't know what we're going to put under the second one. Basically, we're saying they all meet the criteria we discussed above, and then we were going to have to establish a threshold. That's why I think the examples don't really inform us. If we now remove most of the stuff under "Example 1," I think we need to address more what would be the threshold.

MR. HILLBACK: The thresholds are likely to vary between different situations.

DR. McCABE: So do you want to leave the examples to deal with the threshold, or do we just want to discuss the threshold more generally? What's people's pleasure?

Wylie?

DR. BURKE: I think once we start discussing threshold, we'll rapidly get into the question of whether there are different thresholds and what motivates them. So I don't think we need to discuss that beforehand.

DR. McCABE: So do we want to delete these examples?

DR. BURKE: Yes.

DR. McCABE: Okay, so let's just delete these again.

It is time for lunch. I hate to break because -- wait a minute, wait a minute. Just put them someplace else.

DR. KHOURY: But documentation of methods and reviews and stuff, they will be important regardless of what the examples are.

DR. McCABE: That's all in the previous stuff.

I hate to lose momentum with lunch, but I do recognize biological need. Why don't we do a half-hour lunch? Let's take a half-hour lunch. We'll resume at 12:30. But really maybe over lunch there can be discussion of the threshold issues that we will bring back. Certainly, we can't do anything in small groups. But I want to be thinking about how we're going to consider these thresholds, because we've got to get that done within about a half-hour to an hour if we're going to get through the rest of the stuff we have to do today.

(Whereupon, at 12:00 p.m., the meeting was recessed for lunch, to reconvene at 12:30 p.m.)

AFTERNOON SESSION (12:36 p.m.)

DR. McCABE: I'm going to make a proposal. I guess we don't have any scribes, but that's okay. I will make a proposal just for the sake of discussion, and we can quickly discount it if you wish, or not.

DR. LEWIS: You need a computer expert?

DR. McCABE: No, that's fine. We can capture it, depending on what people want. Let's see if people are at all interested in this.

One of the things that came up this morning was concern about were we going to just dismantle the system and then rebuild it. In other words, was the queue going to be so long and so difficult that we would interrupt what is already existing? Recognizing that it is not adequate, or at least it would be my assumption that it's not adequate, that it still is something that's ongoing and shouldn't necessarily be dismantled, and then a two-year queue to get things going.

When we do new residencies, I participated in the establishment of the genetics residency, and you couldn't say, well, you don't have a residency until we get around to you. So everybody who had one was conditionally approved. Could we throw out there, at least to get us through this, that those that exist would be conditionally approved. Then the review group, and we have yet to discuss the constitution of the review group or review groups, would say we will scan through this list of 300 tests that exist, we will use the continuum that Francis delineated for us, and either for those reasons or for others that aren't on that continuum, such as stigmatization, then those will be reviewed first. So we will pick out the concerning ones and review them.

Do we want to go there, or do we not want to discuss this?

Pat, then Judy.

DR. CHARACHE: I would certainly support the concept of the conditional review, but I would like to take advantage also of the structures that exist, such that if the CLIA had this defined list of what you had to look at, as they review the 3,000 labs that are doing these 300 tests, they would identify those tests that are suspect and laboratories that are suspect and perhaps ensure that they didn't continue to offer tests that had never been validated, pending this test-by-test review.

DR. McCABE: Judy?

DR. LEWIS: Two points, one to respond to what you said and one to respond to what Pat said. To respond to what you said, I believe what you're talking about is what I would support, which are two processes, one for ongoing oversight and one for initial approval. What you're talking about is the ongoing oversight piece. I think that makes sense, that we develop an oversight process, and then there become an initial approval process. Those are two separate things.

To respond to what Pat said, I'd just like to support the fact that rather than hook agencies onto it, I'd like to have us look at what we want and then figure out who to do it. It may be that CLIA is the person to do it, and it may be that somebody else is the person to do it. But let's figure out what we want rather than get into which agency's turf it is. I think if we do that, then it will fall out. I don't want to get into figuring out which is the right agency, because I don't know that I know it all. I want to focus on what it is we want to do.

DR. McCABE: Does anybody disagree with that?

DR. BOUGHMAN: I have something I want to present. I spent some time trying to figure out where we were in the bigger scheme of things earlier today, and this was my chicken scratches on a piece of paper

that's been translated here. We had talked about the different phases of a test, and there have been several references to this in the several minutes.

First of all, a test that's in a research phase, we have the transition from research to clinical, which is where we were focused right before lunch. We had then talked about general clinical use and mechanisms related to that, and it might be multiple labs that are using it or totally open use. We've had several references to off-label or a change or extension in the use of a test. We've talked several times about tests already in practice that have not gone through a systematic review in a context. Then I threw in pharmacogenetic because I didn't know where else to put it right now.

We have been focused on the what and how, and, Judy, I think you're right, that those are the questions that we really want to be asking, and I think we all have a sense that's where we want to focus. But, in fact, my proposition is that we don't need to totally reinvent these wheels, which comes back to the fact that there are agencies or some processes already out there functioning. Let me focus for just a minute on the research side.

We had talked about it being the IRBs that would be on the subject protection side. But, in fact, research is also monitored, if you will, by the peer review literature and publication process. We had talked about evaluating protocols, informed consent, maintaining records. It was referred to as good practices before, and what here is in the bold or italics is one of the mechanisms by which that information gets to other people.

In transition to clinical, I put down the FDA here, not because that's the right answer to all of these, but when a sponsor is bringing a new test forward and saying this is ready for clinical use, the way the world functions now in new tests or kits or whatever, those are the ones that the sponsor sends to the FDA.

The star is here because there's a whole lot of information that we've already put down on other sheets of paper when I just said information to be collected or to be reviewed. We talked about thresholds to be met, and we need to get a feel for where we are there. Then we had also talked yesterday more about the data that could be required to be collected, whether we call it post-market or for the CDC or whatever. One of the ways that the rest of the world is protected or understands what's going on is through a labeling process.

Then once we get things into use in a broader arena, what I was thinking then is the CLIA and the clinical review processes, whatever those are -- those aren't as straightforward as CLIA might be. It's at least not one organization, but we had talked about there being lab practice parts of this and clinical practice parts of this. I think there's a lot to be discussed there yet.

I was thinking that under limited use, you could still require data collection. Once it's to open use, we could go to the matrix, and wouldn't everybody like to join in and give us at least the aggregate data, but we're out of the range of being able to require things anymore.

Except that it's in the open use or possibly in the change or extension of the use that the preventive health care consortium model started coming back in. There had been several references to that kind of set-up. Then we had just mentioned, and I think this is where you were coming from, Ed, that for tests already in practice, there could be a group name that would scan these and do primarily literature review or some of the passive data collection mechanisms that Muin talked about yesterday, and that type of group would

develop a report mechanism.

Let me say that all I've tried to do here is put down a framework and try to figure out where I think we are. We can rip this up and not look at it again. But I was getting so bogged down in what questions we were asking of whom, and especially with our limited time -- and I repeat, the who may not be right, and the whats and hows are really just nuggets of the discussions we've already had. One of the suggestions we might have is that we talk about different, smaller groups of us trying to draw the matrix or figure out what the boxes in the matrix might look like
or how they get filled in.

I'm going to take this off the overhead.

DR. McCABE: Wylie?

DR. BOUGHMAN: Don't take it off the overhead yet? Okay.

DR. BURKE: I actually think this is very helpful and moves us forward, and I actually would propose that we do continue talking about the who and the what together, recognizing per our previous conversation that the what comes first. But I think as we get through, and I think what you've already done for us, some discussion about the "what is," it's very useful I think to then concurrently say, oh, this already fits with what's already happening by certain agencies.

In that context, it seems to me what I've heard, and maybe this is a point of discussion, is that there is difference according to whether it's a home brew or a kit as to whether FDA is the who in that first box. It seems to me that we've talked about uniformity of standards. Maybe we should have that in the context of who.

The other point that I would make, and I think it's another useful point of discussion from this model, is that where you've put the role of the consortium makes a lot of sense to me. What I think also is implied in your structure is that the consortium must be a very interactive collaborator with both FDA and CLIA, and it may well be that there should be a deliberate coordination of effort up front. That is, there is an approval process, and it may make sense that FDA has the primary responsibility for that, but that part of that approval process is a sort of clear delineation of the transition to CLIA supervision of laboratory practice, but also a delineation that would come at the point of initial approval of what kind of data is expected to be collected.

Again, that should be a very coordinated effort between, presumably in that case, FDA and the consortium. But I see that we're talking about three entities that need to work very cooperatively together, and to do that we need to define the system well.

DR. McCABE: Other comments? Pat Charache?

DR. CHARACHE: I think Wylie has described it very sharply, what we have to do. I almost think that the question of what to do with tests that are already on the market is a subquestion which can almost follow the discussion of how the rest of this should come about. I personally am deeply concerned about an awful lot of garbage that's out there. So I hate to use the word "conditionally approved." I might just say "conditionally permitted to continue," but I almost think that's a separate question that should come

later.

DR. McCABE: That's what I think. This focus is much sharper than where we were this morning.

Let me tell you the timeframe. We're going to discuss this and any ramifications of this until no later than 1:30, and then we're going to go to the questions. So no matter where we are, we're stopping at that point in time, because we've got to get the questions answered. If we get back to it, that's fine.

MS. BARR: But doesn't this answer the questions?

DR. McCABE: Not really, because we still haven't discussed -- I mean, on that sheet with consortium, we haven't discussed what the consortium is. We have to have some structured answers to the questions.

Elliott?

MR. HILLBACK: I think by jumping and starting to name names, we've gone backwards to where we were many times this morning, which is to say, what is it we really want to do, and is that a suitable organization then to do that? I think, as we discussed several times this morning, if what we're trying to do is figure out what are the hurdles that a test, before it goes into clinical practice, needs to jump over, we have someone, whether we have the skill to do it here or whether that's a role for this consortium we create that has a lot more laboratorians -- but a lot of the people who are on the practical side of the business, as well as the regulatory side of the business, to say how does this work? What are the hurdles that have to be jumped over? How do we assure that they get jumped over? Do we do the same for every test, or do we do different things for different tests?

To start sliding in, well, since FDA is good at making people jump over hurdles, let's put them in the hurdle business --

DR. McCABE: Well, what if we do what Joann just did and we wipe out the who? But at least we look at what the steps are, because she's gone well beyond where we were with the steps. I think that those steps seem to be pretty logical and pretty reasonable.

MR. HILLBACK: This is the process by which things happen. I think that's fine, and to look at what is it we want to try and show at each step along the way. I sure don't want to say when you go and add another mutation to a CF test, that it's going to go back to ground zero and start all over again. There are certain hoops that have to be jumped through when you do that just the same, and I do think we have to deal with this issue of 10 or 20 or 30 labs all doing the same test. There are certain situations where no one would ever be first if being first meant you went through one channel and everybody else went through a different channel. So there are a lot of practical issues that we'll have to look at.

DR. McCABE: Pat Charache, and then Joann.

DR. CHARACHE: I think we can almost turn these into the four phases of testing which we've talked about also and which the FDA uses. Phase I would be this IRB business, which is where the test is developed. Phase II, when you're in limited use, that would be Phase II. That would be transitional clinical, the limited use. Limited use would be first Phase II and then Phase III. Open use occurs at that point after Phase III. Then extension of use is your Phase IV, it's your post-market. So that these actually

fit conceptually into the same structure if one put a dotted line in two places.

DR. McCABE: Joann, and then Wylie.

DR. BOUGHMAN: I just wanted to tell you what other handout you had in front of you for those of you who are not familiar with some of the FDA processes. What we have handed out to you is the in vitro diagnostic products for human use, and this is essentially the labeling section of what an FDA review panel actually goes through. For example, I would take you to the second page of text down at the bottom, number 3, where it requires a summary and explanation of the test, including a short history of the methodology with pertinent references and a balanced statement of merits and limitations of the method or product. Then it goes on.

I asked Steve if he could get this over from the FDA just to let you see, in fact, some of the things that are already out there on the table on the process that any one of the in vitro diagnostics anyway goes through.

DR. McCABE: Wylie?

DR. BURKE: The one point I want to make is sort of a point of clarification and making sure that I understand it. Research, transition to clinical -- limited use could well be, if I'm understanding it, or rather limited and open use both refer to limited indications, I believe. So if we were saying BRCA1, open use would be the point at which we've released it for use with high-risk families, with caveats about sensitivity, let's say, and at that point there would be the process of thinking through whether there's an expanded group of women who might be candidates for testing, and what we are adding in our discussion to what may have already been present is a systematic method of data collection to accompany that expanded use. Is that correct? Am I understanding that correctly?

DR. McCABE: Yes. I think that the concept of open use, it might be open use within a specific population or whatever. That's certainly within the constraints of genetics.

DR. McCABE: Elliott, and then Barbara.

MR. HILLBACK: Who are you going to release for open use? Is this the physician that prescribes the test? You're going to tell them now you can prescribe it for this group? Or you're releasing the lab?

DR. BURKE: Oh, I think the physician, the person who is ordering the test is clearly a target audience. This gets, obviously, into the tricky question of what kind of information you might require the lab to have documented, and that will depend upon what the limited indication is. I think that's going to be a tough question.

But I think everything we've said here suggests that most genetic tests, if we want to get them to market in a timely way, are going to come to market initially with a limited indication. Usually that limited indication is going to be clinical use in a certain circumstance which is most often going to be a certain circumstance of family history.

DR. McCABE: Barbara?

DR. KOENIG: On the same point, the issue that you gave of the expanding populations for BRCA, for

example, is one kind of an example. But what if you had a fundamental transformation in the use of the test, for example, from diagnosis to prediction or to predisposition testing, or into prenatal use? I mean, I think that may, in some cases, be a big change. In others, it's going to be a relatively small change.

DR. McCABE: I don't know that we're going to be able to resolve all of these. I mean, part of what we have to come up with is a way of deliberating these issues outside of ourselves.

Wylie?

DR. BURKE: I think that's a good point, and it seems to me the real issue is red flags. In other words, a test that hasn't been used for prenatal diagnosis and now is going to be used for prenatal diagnosis might be a red flag, because that's a fairly dramatic transition.

DR. McCABE: Pat?

DR. CHARACHE: I actually see a value of the consortium of the type that was under discussion moving up further as well. I think it can be extremely helpful in providing guidance and requirements further up the line.

DR. McCABE: Well, in terms of general structure, can we accept this as a general structure framework that we can now begin to -- the fact that we crossed out the who I think says that we need to start talking about the who, and that will begin to address our questions also, because that really gets into Issue 4. I'd have to look back now, but it doesn't matter. We need to just really start working on it.

Yes, Pat?

MS. BARR: I'm playing with the grid as well, and I just added a column of what's needed. For instance, we have had this discussion of the home brew versus the kit, what is in the consumer's interest, and I don't think that's up there so much, and that's a discussion that we have to have perhaps in transition. It's a transition discussion.

DR. McCABE: So you had another category between oversight and the last column that was --

MS. BARR: Yes, I called it "What's Needed."

DR. McCABE: Okay. Why don't we make some notes and we can add that.

Elliott?

MR. HILLBACK: Can I go to a more general comment? It seems to me that the process that we ought to be trying to do to make a recommendation on oversight, which is I think where we're going, is to go back, for example, to this threshold point and to make the key points that we feel need to be made without trying to do the detailed work. If we really believe that what we want to suggest is a consortium of experts in laboratory practice and the regulatory bodies in a real working group, figure out how to push organizations that are developing tests or ready to take tests into the clinic to do their homework, to do some homework in a certain way, and to then come up with a method to make sure that homework is validated. It may be post-launch, pre-launch, whatever, and with some pressure that that be done in a

timely way, that it doesn't form big constriction points.

Is that what our recommendation to the Secretary needs to be, at that level of altitude, or do we need to be down to the level of here are all the things that need to be looked at, here's who we think ought to do this at every step of the way? I'm not sure that we're equipped, this group in this room is equipped to do the level of detail that we try to do sometimes. Maybe we should be back to is there a process we recommend, and the cautions, the pros and cons at each step along the way, or the major points to consider along the way.

DR. McCABE: I think that one of the things that we got out of the discussion this morning was a lot of those issues, the big issues, and that there's the axes that we described, and I think that those still stand. But I think that there are some other issues that come up, and certainly we spent a lot of time on stigmatization this morning. So outside of those axes, there are other variables that could bump a test up as well.

Wylie, and then Francis.

DR. BURKE: I want to say two things about level of detail. I agree with the basic point Elliott is making, that we shouldn't micromanage, I guess. On the other hand, I think it's really crucial that we have discussions about criteria by which tests are judged, because it's clear that we are bringing social issues to the table that have not previously been brought, and I think that's part of our mandate. It's really part of the task, it's part of why this committee exists.

As a minor point, I would say as we go along and have heard information that makes us understand how FDA participates, how CLIA participates, I think it's appropriate that we should use that information. In other words, I don't think we should ignore that. I think it's appropriate and will be ultimately time-saving if we're able to say here's our larger structure and here's where it makes sense that FDA fits in, here's where it makes sense that CLIA fits in, and here's where we need the production of a new body that interacts with those two. I think it just saves everybody time.

DR. McCABE: Francis, and then I think we've got to get back to the body, because we've sort of made a transition and assumed one of the oversight mechanisms, which is the consortium, and yet we had mixed reviews on that. So I think that it's necessary to get back to the body.

But, Francis, please go on.

DR. COLLINS: I guess I was going to respond to Elliott. I think we have to be careful here that this committee doesn't yet become another example of the task force on genetic testing, that we sort of get to a certain point and then pass the buck once again to another entity, in this case a consortium that doesn't quite have a defined role and nobody is quite sure it's going to work. I don't think that's what you were actually suggesting.

The buck has got to stop here. If we come up with a plan where clearly we pass the buck, then we've missed the opportunity and lost our credibility. To that degree, we really have to be specific enough that it's really clear what we think the process ought to be and who is going to do it.

DR. McCABE: Thank you, Francis.

We need to discuss the body. But I think we also need to embed in that discussion the fact that the system should stop until that body is formed, because we know that that might take some time. I think we have to be cautious, as Francis has said, that we not just be accused of passing the buck. We do have some mechanisms in place, and one of the things that, if we decide we're going to recommend the consortium, and I've certainly presented my biases here before, I think that the system needs to be organized and there needs to be communication within the various parts of the system.

So that's why I would favor consortium. But if we go the consortium route, we should also say that those agencies that already have regulatory mandate need to be strengthened if we feel they need to be strengthened, so that they can be gearing up as there is discussion about whether the consortium is going to be formed, because remember, we're just advisory to the Secretary, and there will undoubtedly be additional discussions.

Yes, Elliott?

MR. HILLBACK: I don't disagree, Francis, and I don't disagree with you, but I have a problem. We have four hours, and then we have a writer who is going to have a week to turn something around so that we can review it before it goes anywhere, and we're at 10,000 feet. We're no lower than 10,000 feet. We're not into the details, and at lunch someone said either God or the devil is in the details depending on what your point of view is. I feel that we're going to end up picking something that isn't well thought through, and we're going to be either too far away from it or we're going to miss a lot of details and do something that's really dumb.

I think we have a very big set of decisions to make, and I don't see how in four hours plus two turns of a document in two weeks we can have any hope of doing justice to the task. If the task is as big as Francis says it is, which I believe it is --

DR. McCABE: Well, you're slowing us down.

MR. HILLBACK: Okay.

DR. McCABE: If you really want us to move ahead, then you need to -- yes. The key thing is that we aren't going to have the ideal document, but we aren't going to take the typical scientific dodge that I am guilty of in my research every day and say the results lead to other questions. We are going to come up with something, we are going to put it out for the community at large to critique, and then we will incorporate those critiques or respond to them.

We're now going to focus the discussion on whether or not we feel a consortium is appropriate, and what parts of the regulatory apparatus need to be strengthened.

MS. BARR: I wonder, for those of you who have thought a lot about it, if we could just start with a job description for the consortium.

DR. McCABE: Well, I'll tell you what I think we need. The job description for the consortium is really to evaluate a test from the time that we would decide it got on the radar screen, which could be a notification in the research phase, to then following through to the post-market surveillance. I see the purpose of the consortium -- we had basically three responses. There was the response that we needed a

consortium. They were almost equal. There was a response that we needed to strengthen CLIAC and CAP. There was a response that said we needed to strengthen the FDA.

I don't see those as mutually exclusive responses. I think that one can say that there is a consortium that will coordinate this view that will also be able to evolve as our concepts about genetic testing and genetic technology evolve. In my view -- but again, I'm speaking as a member of the committee now and not as the chair -- the key role of that group is to coordinate as well as to evaluate. It's to coordinate the evaluations.

Yes, Judy?

DR. LEWIS: It would help me to have a sense of who we are seeing as members of this consortium besides some of the federal agencies. That would help me. When we talk about the professional community, are we talking about it broadly defined? Are we talking about it narrowly defined? Are we sure that there are consumers involved? Do we have social scientists involved as well as physician scientists?

DR. McCABE: Well, I think that we again got from the responses that if we were to have a consortium, there should be at least four components of the consortium and not defining the various numbers and that sort of thing of that consortium. But it involves the regulatory agencies, and I think that it's important to note on there that OPRR was listed as one of the agencies on that list. I think OPRR could use some education about genetics. So I think that we need to decide whether they should be added. So that's one, the federal agencies, and we can discuss which would be appropriate.

Number two -- and these are not in any particular order -- we definitely heard very strongly from the community that there needs to be community representation, and we can discuss whether those are advocacy groups, public members, whatever, but a group that is community.

A group that is professional organizations, and again we could get into who that might be.

Finally, a group that is the private sector, because I think we would all agree that they need to be represented as well.

So those would be the four components. Then if other people have additional components -- yes, Muin?

DR. KHOURY: I guess I wanted to react a little bit to what you first said about the government agencies that have a regulatory role. I think as you start farming out the jobs, the various categories of what this consortium would do, some of the agencies like NIH and HRSA and 99 percent of CDC are not regulatory but will be terribly involved in the data collection process. So I don't think you should forget those.

DR. McCABE: And I probably misspoke by saying regulatory. But it's really the federal agencies, so strike the regulatory.

Pat, then Victor.

MS. BARR: I'm with you so far. I think that the next question I would have is, given the increasing

responsibility, because we see a wave of more and more and more of these tests, is this imagined as a full-time and staffed commissioned consortium, or is it imagined as a periodically meeting group? I think we should try to give as much clarity about that as we can.

DR. McCABE: Do people wish to discuss that?

Yes, Wylie, and then Pat.

DR. BURKE: I think there's no way to get the level of representation you want without having one component of it be a periodic meeting, something along the lines of this kind of process. But I think there has to be close attention paid to staffing and perhaps coordination by some of the federal agencies. In other words, a group meeting like we're meeting can't get through the data analysis that needs to be gotten through. There needs to be a process of data analysis that then is brought to that group.

On the other hand, a group like this provides a forum for community representation and professional and private representation that I think is very important. Maybe there is some model that blends those ideas.

DR. McCABE: Pat Charache?

DR. CHARACHE: One of the key issues here in terms of answering that question is exactly what the charge is. If their charge is to evaluate a test and follow it through from beginning to end, you're creating a second FDA. The only concerns I have about the FDA is them being swamped and providing restrictions. I think if we set up yet another bureaucracy, we would have the same problems of funding, and time constraints might be in place.

On the other hand, if we defined what the FDA should do, what it does and what it does well, evaluating tests, and what it should do, what CLIA does and what CLIA should do, then we're going to be left with some gaps. An example of gaps is data collection and analysis over time. Maybe another gap is just ensuring that these bodies work as a team. Another gap is providing the information that they lack and the guidance that they lack, and look at the other areas that are not being addressed, like stigmatization.

So I think under those circumstances, you'd have very different need in terms of bureaucracy and funding, and you'd be defining a much more expanded charge in addition to the bodies that exist.

DR. McCABE: Since I threw out the model, I'll just clarify. I was not saying a parallel bureaucracy. There are agencies with statutory regulatory power, and I think that to dismantle those would not help us accomplish. But I think that we need to strengthen them. We need to look for the holes and determine how those holes will be filled in.

Victor?

DR. PENCHASZADEH: Pat Charache just outlined some of the things I had concerns about, because if there are indeed statutory regulatory agencies with a clear mandate, I'm concerned that creating a new body, or call it whatever we want to call it, a consortium, might in fact dilute the authority that these agencies have today. So it's a little bit contradictory, on the one hand saying, well, we'll enhance their role in particularly addressing their shortcomings in terms of expediting and streamlining reviews, and on the other hand saying, well, we'll give some tasks to another body.

I do agree, I like the idea of a consortium, but I see it more in the lines that Pat Charache has outlined: coordinating, incorporating community representation, professional organizations representation, the private sector representation. But I would be very careful to not dilute the regulatory power that the current agencies, the federal agencies have. So I think we should be very specific about what charges we would give this consortium.

DR. McCABE: Joann, Pat, and then Francis.

DR. BOUGHMAN: Periodically, as we go through the next couple of hours, imagine yourself sitting in the seat of the Secretary or the Surgeon General. What is it that you need to hear from these folks out there that are talking about this?

In the Secretary's position, there are the resources to in fact configure a new organization if we give them the charge and say it is these groups. I'm not sure that any other person would have quite put together the same people around the table, but we've been able to balance and fill in and have a lot of give and take.

It seems to me that if I were the Secretary, I would want to hear something to the effect, at least a few of the following things. We know that we're on the cutting edge in genetics. We know that the current system is not up to speed. We know that we need to look at this anew and in long term, because we are advancing so rapidly and with such expanding information.

These things are being done okay now. Here are the gaps in the system as they exist from what we have learned, and one of those gaps is the issue around social issues, stigmatization, and so on. In fact, not only on the consortium, but I think we can be pretty specific about the need for appropriate representation on some of these other bodies as well. On the FDA review panels, there is a consumer member, but it is not deemed that that consumer member needs to have any special kinds of expertise. In fact, we might consider that the consumer member might, for any one of these groups, represent or be approved by some group.

Furthermore, even in the CLIA practices and when they talk about the inspectors, it could be that there might be an observer that is involved somehow that represents the process, bringing to the table recognition of these issues. To me, that would be an appropriately strong statement and give some action, some meat to chew on and actually create some action that would provide useful outcomes.

DR. McCABE: Pat Charache, then Francis.

DR. CHARACHE: As I say where the consortium might be a strongest contributor, I want to ensure that my view is clear, which is that this consortium should have a permanent structure. It shouldn't be an advisory body that meets once a year. I would see it, for example, as helping to decide when a given test needs FDA attention promptly, either because it's a defective test or because it's of great importance. I think that rather than the FDA's current position, which takes things as come in in turn, I think a body of that type could be a triage center. I think we can define its activities as extremely important and productive.

DR. McCABE: Francis?

DR. COLLINS: I guess this still seems to me pretty difficult to imagine implementing, and I still have

not heard a clear justification for the role of this consortium. I'm trying to understand this, believe me, but I'm not sure I can see it.

If we already have statutory authorities that are vested in certain parts of regulatory agencies that could be applied to this problem, why should we not first figure out what they can do and then see what the gaps are, as Pat said? I'm not sure I'm convinced there are going to be a lot of gaps. Some of them might actually be filled by this body here. This committee is not expected, as far as I know, to necessarily disappear after today. If we're talking about a group that aims to coordinate consumer points of view in various government agencies, we're all sitting here, and let's not try to duplicate that effort if we don't have to.

So, again, maybe there's something I'm missing here, because it doesn't seem to me that I've heard the case for what this consortium is going to do that could not be done by the CLIA system plus the FDA. Maybe I'd rather we talk about that first, and then see what's left.

DR. McCABE: Kate, then Pat Barr, then Wylie.

MS. BEARDSLEY: I think what I was going to say has already been said. It seems to me that if we're talking about a consortium that has regulatory authority, we're in deep trouble, because I think it would be really hard for a consortium to regulate, let alone whether we needed to regulate.

If we're talking about a consortium that's coordinating, and particularly one of the gaps I think, Francis, is the data collection effort. It seems to me that from that perspective, the consortium is perhaps a very good idea. That's something that, as far as I know, we don't have a federal agency that's doing that right now.

DR. McCABE: Pat Barr?

MS. BARR: I think my sense of the consortium is to take the working group that has been created -- it's my understanding that the agencies are trying to communicate and talk together to address genetic issues, and some of that came out of the reports that were done before we arrived. To look at that group and say would there be a benefit to adding some professional organizational reps and consumer reps to that particular group so that, as they proceed and they work on these issues, that particular voice is heard.

But I had always imagined it as being built on this coordination effort that's already going on, and that we might add tasks to that as we go through this list. I think they've already started talking about what each of them can do.

DR. McCABE: One of the things that I'd like people to be thinking about talking about is Francis' suggestion that we are the coordinating group, rather than building another structure.

Wylie?

DR. BURKE: Just following up on those comments, I think there are two tasks that we have talked about under the heading of consortium that aren't clearly already being done or potentially could readily be done by FDA and CLIA, and I think our structure is clear enough that I think we probably should be clarifying now, very soon, exactly what FDA and CLIA are doing and can do.

MS. BARR: CDC, too.

DR. BURKE: Yes, let me get to CDC other than CLIA in just a moment, because I think the two pieces that we can already see are links that need to be filled are, number 1, an advisory capacity that might aid in prioritizing. As Francis said, that's what this body is doing now. It would be an advisory capacity that includes the appropriate input from the appropriate different stakeholders, including private organizations and community.

I think that could be accomplished either by sustaining a body like this or potentially folding that kind of advisory capacity into FDA and CLIA procedures. But I think that role and that multidisciplinary and community input needs to be there and needs to continue. It's an advisory capacity. It's not new regulatory authority.

The other, which I think is quite different, is that we have had a lot of discussion about the need for a much more structured and rational plan for defining the data that still isn't there at the time of initial limited approval, and therefore the data that needs to be collected on an ongoing basis. There I think we need to think about federal agencies involved in surveillance, and this clearly, I think, points to a role for CDC other than the CLIA CDC role, but I think probably is best accomplished by a consortium that includes NIH, includes the prioritizing process that might lead to RFAs in areas of critical data need.

I think it's got three pieces. It's defining the data that's needed, it's facilitating that data collection and analysis, and it also includes an authoritative source of data, using that concept of getting things up on the Web in an authoritative way in the public domain.

DR. McCABE: Barbara, Michele, Judy, and Victor.

DR. KOENIG: Very quickly, I just want to second what Wylie said. I'm in total agreement.

Then to follow up on what Francis said, I think the other area that's missing right now is some kind of a group to address the social issues in a proactive way, and that is something that perhaps some of the existing federal agencies are actually prohibited from doing because their focus is more technical. Someone correct me if I'm wrong, but I think that is one unique role that is now not done that this consortium could do, and could do at many of those phases, in particular from the research to clinic phase, which is one of the most important ones.

DR. BOUGHMAN: Can I just respond to that?

DR. McCABE: Quickly.

DR. BOUGHMAN: I just wanted to say that, in fact, in the FDA process, some of the issues are handled, and let me give you an example that's not genetic, and that is moving from prescribed to over-the-counter, where there is a tremendous amount of discussion that goes on about not just the labeling but the potential advertising and the educational pieces that go along with it; reading levels, access.

DR. KOENIG: That's not the kind of social issue I'm talking about. I'm talking about more the issues like impact on groups, that sort of thing.

DR. McCABE: Michele, Judy, and Victor. Then what I'd really like to do, again, we need to do some things that are concrete. So unless people have very strong objections, after Michele, Judy, and Victor, I'm going to then propose that we basically take a vote on Francis' proposition that this is the consortium. So be thinking about that.

Michele?

DR. LLOYD-PURYEAR: I, like Muin, keep going back to immunization experiences because it's a model that works, and it's similar to what Francis is saying. There is a national vaccine advisory committee which is essentially this, plus some more government agencies, and actually more professional and consumer groups too. They look at issues and they help develop policy, and they're answerable to the Secretary.

But also, within the immunization groups, that program, FDA does collect data, and it's an ongoing data collection, and it's actually within the law that created all of this, it's a mandatory data collection that the physicians are supposed to report that data to FDA. So there is a system that's set up. It doesn't have to be mandatory, it can be collaborating, and it's a fairly effective model.

Again, I want to echo that I don't think we need to create a new regulatory agency, and I think the FDA and HCFA both have the kind of regulations that are already in place. They just need to be enforced.

DR. McCABE: Judy?

DR. LEWIS: I think Francis captured very nicely the idea of the fact that we could very well be the consortium, because we represent all the perspectives that I heard you say. I think the other thing that we've got going for us is that, at least the feedback I've gotten from our meeting last month is that we've gone a long way to try to connect with and do the outreach and begin to build some trust with the communities. I know we're not there yet, but I think the efforts that we took last month in terms of outreach and in terms of involving the steering committee gave us a sense of credibility with the communities.

If we start to have that outreach on an ongoing basis, I think it may well be that we can do this as this group. So that was a very attractive idea, and I don't like the idea of a committee creating another committee.

DR. McCABE: Victor?

DR. PENCHASZADEH: I just want to echo what Judy and Michele just voiced. If we are thinking that we have two agencies that have a legal mandate, then the role of a consortium gets more and more diluted, in my mind, because you have issues of accountability, of who does the consortium report to, what are the legal mandates. So in my view, it would seem to me, and perhaps people from CLIA and FDA who are here could tell us when we get to answer the specific questions, what is preventing them from really enforcing all the authority that they have by law, and particularly I'm referring to the genetic testing services.

DR. McCABE: Okay. With that, I want a motion on the floor. Francis, it was your idea, but certainly if Joann wishes to amend it, you can decide what is appropriate.

DR. COLLINS: Okay. I'd like to amend it myself because I'm a little worried about the way in which it was taken. Basically, I was not proposing that there might not be some role for a consortium. I just had not exactly heard it defined. If the role was to be a coordination effort and an opportunity for consumer voices to be heard, as well as federal agencies and other expertise, it seems to me we have that here.

So I guess my motion would be that if there is a need for a coordinating body to deal with the issue related to genetic testing, and to include consumer voices and the representative federal agencies that have a stake in this, that we not duplicate the existence of this committee by creating another one. That does not rule out the possibility that there might be some other role for a consortium that this group could not do. I just haven't clearly heard it verbalized yet.

DR. McCABE: Can I have a second for the motion?

DR. COLLINS: It was a little long.

MR. HILLBACK: Second.

DR. McCABE: Is there a second? Was that a second, Elliott?

MR. HILLBACK: Sure.

DR. McCABE: Okay. So we have a motion, and it's been seconded, so now let's discuss that motion.

Joann, I'll let you.

DR. BOUGHMAN: I'm sorry. I was going to approach it the other way. Given that we have this committee with a charge that is ongoing, given that we have a work group that has been started, now given that we have defined the components of this consortial- type group, I was going to make a more active motion that, in fact, the work group that is a working group created by this committee, as I understand it, or at least affirmed by our committee --

MS. BARR: The Secretary did it. It came out of the testing task force.

DR. McCABE: Please speak into the mike.

MS. BARR: My understanding is that it was a recommendation of the genetic testing task force and the Secretary moved to do it because of that. So it existed when we came to the table.

DR. BOUGHMAN: Okay. Then maybe rather than making a motion, I'll just turn to Francis and say, Francis, could you word your motion in such a way that this committee be maintained as the overarching coordinating or whatever body, but the work group somehow could provide us data, and that work group might have the other components represented on it?

DR. COLLINS: I'm not comfortable suggesting that we endorse the existence of a group whose functions aren't really clearly stated, because I don't understand what the work group would do.

DR. BOUGHMAN: Okay.

DR. McCABE: I have Elliott, Muin, Pat Charache, and Wylie.

MR. HILLBACK: Okay. Let me go back, because the concept of a consortium, the first time that was used was in the small workgroup that worked on the various options, and the concept there that we had was that, again, to go back to the devil's in the detail, that if it's the sense of this committee eventually that we need to get into setting of a lot of details and a lot of detailed standards of some of the things we talked about -- I mean, Joann's outline on oversight lays out the sequence of events, and at every point in there, there are 100 or 200 things that have to be done.

So the concept at that point in time, when we had those multiple phone conversations back in the fall, was that a subset would be created that would be set up to be ongoing that would work on those details on a regular basis to define the needs at each step and then try and figure out what was the best way to do those, and that the role of this group in setting the guidelines for that would be to set some general direction, a lot of direction, about what we wanted, whether it was the flexibility point or whether it was the point of every test has to be looked at by somebody outside the lab before, whatever the principles were, but that the consortium was going to consist of people from the laboratory industry, people from the academic side, sort of the Society and College on Genetics, it was going to include several of the agencies, and it was really going to be a working group to originally set the details, sort of the real law, rather than the principle, passed by Congress, which we're more like, it seems to me, of how this would work, and then to monitor that and then to alter it as it went along.

That's where that consortium idea came up. I still think this is the right outline of the process, but we either have to decide that we're going to recommend that level of detail or we have to figure out who is going to do it, and that's where the consortium originally came in.

DR. McCABE: I have Muin, Pat Charache, Wylie, and Pat Barr.

So, Muin.

DR. KHOURY: I have no problem with SACGT being the consortium. As a matter of fact, I like it.

On the other hand, when SACGT was created, and maybe Francis and others can correct me if I'm wrong, one of the things I wanted SACGT to do is to evaluate test by test, and I was being told no, that the function of this group is going to be sort of an overseeing body that will look at genetic testing issues in general.

Now, we're at the point where we are at the detail level, where a framework for both regulatory and non-regulatory approaches to oversight need to be discussed. We need to bless or not bless specific tests. We need to collect the data or ensure a mechanism for that to happen.

So I think that the regulatory pieces of the puzzle are all here in this room. What's missing in the mix is sort of the data component that would help the regulatory process move forward. So I would make another motion that this group considers, at least, creating a data working group that will essentially flesh this out in a more coordinated way.

DR. McCABE: Let's hold that. We already have a motion on the floor, and let's deal with the one we have first, but we can come back to it.

Pat Charache?

DR. CHARACHE: To clarify the question that came up a moment ago in terms of working groups that already exist, the working group that existed prior to this one was the Genetic Working Group for CLIA, but there is a second body that you heard from yesterday, which was initially called a Laboratory-Consortium Group, and then changed the word to "Forum," so they wouldn't confuse it with this discussion that's now on the table.

That group, which does include clinical as well as laboratory people from the American College of Medical Genetics and so on, serves a very useful purpose which is a subset of the two issues that need a consortium effect, and that does address a lot of the key details that have to do with what you need to do to introduce a laboratory test, and does pull together the FDA and CLIA and other groups.

I think that, which would report to both CLIA and to this group, since it was requested that this be done to pull these groups together, is a very useful body. It doesn't replace the need for this level consortium.

DR. McCABE: Wylie?

DR. BURKE: I guess I'm agreeing with what's been said. I respect the fact that the motion on the table is whether we should continue SACGT as an advisory oversight, and I think we need an advisory oversight group to provide the input that is being provided here, whether it's SACGT or some permutation of it.

What I think we just need to acknowledge and it's really important, and I recognize that I'm partly repeating what others have said, is that that solves only one missing link. I think we then need to get clarity on what FDA does and what CLIA does and can do, but I think we already know enough to know that there is a data collection/analysis/dissemination task that is still not accounted for, yet we have identified as critical.

I like Muin's suggestion that we would identify a working group. We don't need to solve exactly who and what and how. We just need to acknowledge that process needs to be part of the picture.

DR. McCABE: I have Pat Barr, Reed, Steve, and then what we've done is we've made sure the computer was all fired up, because I want to write down what Francis' motion is, because it was still a little bit vague, I think.

But remember, what we are doing is we are advising the Secretary. We're advising the Surgeon General. So our advice would be that such a consortium is required, but we feel that at this time, in order to maintain momentum and recognizing the expertise available, that the SACGT could, at least for this time, serve as the consortium.

Pat?

MS. BARR: I was just going to try and clarify that and maybe simplify it. That the SACGT is serving at the request of the Secretary, that we've been asked to review oversight, that we have found a need for ongoing review and coordination, and to the extent that we are able, we are willing to fill that need now, but will recommend that some group continue to pursue it in the future.

Is that a friendly amendment?

MR. HILLBACK: But that's what we are.

MS. BARR: Right, and I think it just --

MR. HILLBACK: That's where we are.

MS. BARR: We just restated.

MR. HILLBACK: There's no need for a consortium. If we say we're it, what are we going --

DR. McCABE: No, but I think the --

MR. HILLBACK: We'll morph into another name.

DR. McCABE: Well, but I think what it is is it's expanding our job description, and so therefore I think that that's the event.

But Reed, Steve, and then Wylie.

DR. TUCKSON: I think it is very definitely an expansion of our job description and for a different explicit reason, and I think that that has to be very clearly stated. I worry about creating or recommending too heavy a bureaucracy, but I really do think that our group will need to be augmented by subcommittee work, and I think we'll discuss later this issue of the data collection stuff and those kind of things.

The only point I would also make is just a sensitization point, and that is that I think it is useful to have those subcommittees because you bring other people to the table who are very key and who are feeling I think maybe even a little left out of this process and who need to have buy in. Particularly, there is certainly a need for more of the medical clinician community to feel more a part of this, and I think that's going to be very important how we address that, and I want to make sure that we're sensitive to that.

So I think that perhaps some of the subcommittee mechanisms perhaps is a way to do it, but I'm real nervous about creating too great a bureaucracy. The data collection side may be a big way to help on that.

DR. McCABE: Steve?

DR. GUTMAN: Well, there are a lot of huge jobs on the table here. It's a huge job to classify tests according to either an old or a new scheme and decide what kinds of scrutiny they deserve. It's a huge job to try and establish standards or guidances or voluntary standards or principles or practices for tests. It's a huge job to decide which tests deserve scrutiny and then to scrutinize a test, and it's a huge job to do the kind of data collection that Muin is piloting, and it's not a job that can be done by the consortium as a night job. It would have to be a day job.

So my recommendation to you would be to ask each of the organizations to devote someone for the six

months of time to come to Washington and to actually do the job if you want them to do that job.

DR. McCABE: Wylie?

DR. BURKE: Actually, for exactly those reasons, I would be very reluctant to call us the consortium. I think this committee or a committee like it that provides appropriate community input and advice and oversight is part of the consortium. I think we've identified a piece that we need, and I think there's another piece that we know we need and we don't know quite how we're going to structure it. I think it's very important to keep that in mind, and that's the data piece.

DR. McCABE: Elliott?

MR. HILLBACK: I agree with Steve. I guess what I was trying to get at earlier and didn't say very well is that I still think there's 1,000 points of detail on this, some of which we have to decide whether we like or not. You know, are we willing to have some tests not reviewed by anyone other than the lab before they're put into clinical practice?

Those kinds of details, until we lay out this entire flow -- and I would maintain it's not just the lab side, that we have to start getting into the relationship with the clinicians and the users at the other side -- until that detail work is done, we don't have a whole process.

I think it's a group of people who are driven by, one, having enough time and enough knowledge of the details to try to come up with the flow of how a test starts in the preclinical stage -- I don't even want to call it research, but preclinical stage, and how it evolves and morphs over time, and what are the checkpoints, what are the jump points, and to do enough detail that we can then say, yes, we like that. That gives a better set of oversight than the combination of what's existing today and it covers some of the concerns that we have.

Until we get into that detail, I don't think we're there, and I think that group needs to be created. It's not just FDA, it's not just CLIA, but they need to be part of it, but it's a real working group to try to put together an approach to regulation with details in it that then has somebody -- we can react to that. It's very hard to react to the general principles.

DR. McCABE: Francis, do you want to state something that we can get on the computer as a motion and then vote on it?

DR. COLLINS: I can try. I confess I'm feeling a little uncomfortable about the appropriateness of this motion, but I'll try.

Basically, let's try this.

DR. McCABE: Before we spend the time on it, let's take a straw vote on the motion and see if it's worth putting the time in to craft it.

The motion is basically that the SACGT become the consortium.

DR. COLLINS: That's not my motion.

DR. McCABE: What is the motion?

DR. COLLINS: We have a real semantic problem here, okay? Maybe we should abolish the use of the word "consortium" for the next half an hour because it means 10 different things to 10 different people.

What my motion was was that if there is a need for an ongoing coordination function that involves the federal agencies that have a stake in genetic testing, as well as a consumer voice, as well as professional societies, that this committee could perform that function. That says nothing about whether we need a data group, which I agree we could not do, at least not in our current constitution. It only says if the goal is coordination between the relevant parties, we have that here. That's my motion.

DR. McCABE: Okay. So we've already seconded the motion.

DR. COLLINS: It's still seconded, isn't it?

MR. HILLBACK: It's still seconded.

DR. McCABE: If we were to vote on this motion, how many would vote aye?

(Show of hands.)

PARTICIPANT: We changed it.

DR. McCABE: Okay. To me, the way the motion is stated is that it pretty much says that we're doing what we're doing.

DR. TUCKSON: Let's go do the work. Let's go to the boxes.

DR. McCABE: Okay. Do we want to start with the questions and go through question by question?

DR. LEWIS: No, we want to fill in the boxes.

MS. BARR: We want to fill in the boxes.

DR. KOENIG: The whose box?

DR. McCABE: Joann's boxes.

Do you want to go up to your overhead?

DR. BOUGHMAN: Sure. What am I supposed to do with it?

DR. McCABE: But we still have those five questions, don't forget.

MS. BEARDSLEY: If we fill in the boxes, we'll know the answers.

DR. BOUGHMAN: Should it be on the transparency or on the computer?

DR. McCABE: One way or the other.

DR. BOUGHMAN: It's on the computer.

MR. HILLBACK: If she needs to write on it --

DR. McCABE: Yes, one way or the other. Let's do it from the computer.

Okay. So where are we going to start filling in the boxes? We were concerned about who. That was taken off the screen before. So let's put it back on and determine who.

Research is IRBs. It's --

MR. HILLBACK: I really think it's the wrong place to start with who, because we don't know what. Until we know what -- we don't know what. We have not argued about is every test going to be reviewed by some organization outside the lab, have we?

DR. LEWIS: Yes.

MR. HILLBACK: We have. Have we voted on that? Have we said that is going to happen?

DR. McCABE: Does somebody want to make a motion?

DR. LEWIS: So moved.

DR. McCABE: What is the motion?

DR. LEWIS: That all genetic tests receive periodic oversight and all new tests receive initial review.

PARTICIPANT: Independent review.

DR. LEWIS: Independent review.

DR. McCABE: Do I have a second?

DR. LEWIS: That's the motion on the one. Then we'll deal with the who later.

DR. McCABE: Do I have a second on the motion?

DR. BURKE: Second.

MR. HILLBACK: It's easy to make the motion. To think through the implications of what you're saying is not so simple.

DR. McCABE: Okay. The motion has been made and seconded. Now let's discuss it.

MS. CARR: Wait. Do you want it up there? Should the motion be on the screen?

DR. McCABE: I think the motion was pretty straightforward. It can be captured from the tape.

Yes, Pat?

DR. CHARACHE: I would like to see all tests that are out on the market also reviewed.

DR. McCABE: She says that.

DR. LEWIS: That's my concept of ongoing oversight, oversight of existing tests, which means you get to look at them, and then review of all new tests. I was assuming that was what I meant by oversight.

DR. CHARACHE: I'm looking at this as not quite the same, but if you say that the oversight includes the requirements for the new test.

DR. McCABE: I think it's there.

DR. CHARACHE: Okay. Fine.

DR. McCABE: The way I heard the motion.

DR. CHARACHE: That's fine.

DR. McCABE: So is there further discussion or do we wish to vote on this motion?

MS. BARR: Call the question.

MS. BEARDSLEY: Wait. I have a comment. Can I make a comment?

DR. McCABE: Quickly.

MS. BEARDSLEY: I have a lot of trouble knowing whether I want to have an outside review when I don't know what that review is going to accomplish, what the standard or the threshold is that's going to be applied to that review.

DR. McCABE: Other discussion?

(No response.)

DR. McCABE: All in favor of the motion as stated, please raise your hand.

(Show of hands.)

DR. McCABE: Are we counting? Is staff counting? Oh, we're filling in. Please hold your hands up high.

All opposed?

(Show of hands.)

DR. McCABE: Wait a minute. We need to get the opposed. Two.

And any abstentions?

(Show of hands.)

DR. McCABE: Two abstentions.

PARTICIPANT: Who was the second one?

DR. McCABE: Joann.

Can we have the votes just formally for the record?

MS. LAWSON: Eight for.

DR. McCABE: Eight for the motion, okay.

MS. LAWSON: Eight for the motion, two against, and two abstained.

DR. McCABE: So the motion carries.

MS. LAWSON: You didn't vote.

DR. McCABE: Well, I'm voting in the case of a tie.

MS. LAWSON: Right.

DR. McCABE: So that motion has been made. Now, what is the next issue that you want to take up? We're trying to fill in this, this grid.

(No response.)

DR. McCABE: We're all done?

MS. BARR: No.

DR. McCABE: Okay, Pat.

MS. BARR: I think the next one that I would like to address, frankly, is the Phase II who, and I'd like to address it using the worksheet that we had produced this morning where we talked about criteria for review, different types of tests, and I guess those two long lists.

While FDA is up there now, I am not convinced that FDA can make this simple enough to not overburden a system that seems to be working for home brews, but needs some review, and so I'd be really interested

in what David has to say about what might be possible, and then hear what CLIA thinks would be possible.

DR. McCABE: David?

DR. FEIGAL: The average -- I mean, the kinds of things that you have suggested that you'd like to see addressed include many things that actually we don't require. So if the issue is burdensomeness of the process, you've already outdone us in terms of some of the things that you've suggested need to be evaluated.

Some of those are the obvious things, like some of the social kinds of settings, but other things, for example, are things like a comparative standard. That's not something that's required for marketing approval of any type of product in the U.S. In fact, we have a preference for absolute standards, rather than comparative standards. In drugs, that would be the placebo-control trial. In devices, it's against some type of diagnostics. It's against some type of gold standard.

This is an area where we typically handle about 4,500 applications per year for 510(k)s. The issue would be sort of how many of these would slip into the PMA area, some of the areas, and the law sort of already says what our review mechanisms are, and some of those would require preapproval inspections, if it falls in the PMA, things that would not just increase the burden for us and for others.

But on the other hand, if you don't use us, no one else has any authority to take any type of action for someone that wants to ignore. The IRB has local authority. It has authority over its own institution. A national IRB has no authority, for example, if you think of that kind of setting. So you also sort of have to think through the logic of -- and CLIA has authorities.

But I think that what our approach to this would be, and I apologize for having to think out loud a little bit, would be that there are probably a number of these areas where we could establish standards, where we could say these are certain types of problems that need to be addressed and these are ways of approaching them, so that if a laboratory was going down a well-trodden path, whether it's a manufacturing path or whether it's a way of dealing with genetic counseling, there would be a way to point them to common ways of solving the method, and then if they assert that they're conforming to the standard, then that decreases the application burden for them and it simplifies the review process for us.

So there are tools that we can use to streamline processes that we've done in other areas, but we anticipate this is an area we're going to have to get into. In fact, it's in our budget request for next year to increase our resources in this area, so we're anticipating this is something we need to get more engaged in.

The other comment, which isn't as much of a challenge for you as it is for us, is that as you move into home brew in this area, we have to think how does a fence get drawn around just this home brew? Let's say, for example, your previous vote were to be something that was somehow enforceful, does this imply that every home brew can't be offered unless there's an IRB review of the home brew?

There's also quite a discussion these days about how well staffed, certified, and up to the task are the nation's IRB systems, which are not well funded, not certified. They have a lot of good things about them, but they also have their limitations.

But I think that this is an area that if it was a commercial product, it's definitely ours. We would definitely do it. If it's home brew, I think we would look at ways of using standards to try and simplify the process. If legally these things fell into the PMA category, there would be some things that would come through that would be hard for us to waive. They're just part of the law.

DR. McCABE: Let's have Judy Yost respond for CLIA, because that was the other part of your question.

MS. YOST: I'll try and be as brief as I can, and please feel free to ask me any questions.

CLIA, of course, already regulates every test done on human beings in the United States now, just as a baseline.

CLIA has five basic quality components in its conditions and standards for testing, and they include quality control, routine quality control; personnel qualifications; proficiency testing for all tests, some of which is regulated, some of which is not.

They also require what is called patient test management or basically a record-keeping system, which includes confidentiality. It does cover all the three phases of testing: preanalytical, analytical, and post-analytical.

It requires a quality assurance program, which is basically an ongoing process to monitor the total testing process, so that you're looking at the entire testing operation to ensure that quality results are produced, and that's probably the key thing because it ties all the other technical components together, and that's your connection to the patient at the other end, is to ensure that those quality results are provided.

Included under that umbrella is, of course, the concept of analytic validity, which it does do. It requires that there be accuracy, reliability of precision, specificity, sensitivity, and a reportable range for the test.

And that's essentially what we assess on the laboratory every two years on an onsite inspection. The requirements under CLIA currently are built on what is called test categorization as the basis, meaning the more complicated the test is to perform, and many genetic tests fall into the highest category, the more stringent the requirements.

DR. McCABE: David, did you have a follow-up?

DR. FEIGAL: I just wanted to make a comment to emphasize something I think that's a difference in our two missions, which is your focus is on the laboratory every two years.

MS. YOST: It's the lab.

DR. FEIGAL: Whereas ours is on the tests as they come up.

MS. YOST: That's correct. We do not regulate manufacturers or test procedures. We regulate the laboratory, the performance of the test in a particular environment, regardless of where it is.

DR. McCABE: I think one of the issues that we've discussed, and just to bring up in terms of test/laboratory, that we've been concerned about how the patient fits in to all of this, and I think that's one

of the roles and that's one of the things that's been brought out by the public comment, and that we need to think how we can strengthen that concept, which has to do with the clinical piece as well.

I have Elliott, then Francis.

MR. HILLBACK: Nothing right now.

DR. McCABE: Francis?

DR. COLLINS: I wanted to ask David to be a little more explicit in terms of the FDA model. I appreciate your indicating that FDA is not only interested in potentially taking this on, but has even thought about asking for some budgetary help for it, because I'm sure this is going to require a fair amount of time and effort.

But if you were to take on the evaluation of a new genetic test that is not already out there -- so let's try to make this a little simpler -- and one of the ones which this group or some other decisionmaking body -- hopefully, this group -- has sort of identified as one that needs particularly high scrutiny, obviously, according to the model up there, information would need to be collected for you to review before that test moved into clinical practice.

My expectation would be that that data would normally be the responsibility of the laboratory that wants to market the test to supply, and is that correct, and in that regard do you see a need for an additional data gathering group that would be separate from that laboratory, or would you expect the laboratory that's applying for permission to market the test would be in the strongest position and the most highly motivated to collect that data for FDA to review?

DR. FEIGAL: Well, for initial market, they'd be the most highly motivated and it's their responsibility, and the laboratory is the manufacturer from our point of view in this kind of a setting.

It all depends on the claim that's being made. What they could say about what the test can deliver, it's an evidence-based decision. That evidence could come from the literature. It could come from their own data. There may be things that, if they can reliably detect a gene, if we go back to our sickle cell example, and say we want to substitute this in to take over the role of an older test, but be used in the same way, then they can rely and bridge very heavily to the older tests.

I think the incentives for longer term data collection in some of the predictive tests or predictive areas and things, often there isn't a lot of incentive for the manufacturers to develop that. That kind of information often develops in the literature, and they may not ever come back and ask to have their claim changed for that test, and that's not just true of diagnostics. It's true of therapeutics. Often the long-term consequences of a treatment are often studied in the post-market, often studied by NIH or cooperative groups, or other kinds of settings. That kind of information can be used to change the label and sometimes it's done even without a request from a manufacturer, but clearly it kind of depends on the environment, whether there's an incentive for the manufacturer to go after that information or not.

I think that's one of the things that's a criticism of using FDA as the tool for medical progress, if you will, is that the main incentive is that first entry into market, and then once you're there, the incentives change quite a bit.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: This is just a little bit of a reality test. There are 4 million babies every year who are tested in newborn screening programs. CLIA, what kind of oversight do you offer for those labs?

MS. YOST: As far as frequency or size?

DR. LLOYD-PURYEAR: Well, I mean, they do not necessarily have CLIA certification, and in fact -- well, they use a CDC lab that is not CLIA-certified for their proficiency testing.

MS. YOST: If they're doing human testing, they should be certified. We do certify a number of labs at CDC currently.

DR. LLOYD-PURYEAR: Well, you don't that one.

MS. YOST: Then they're out of compliance.

DR. LLOYD-PURYEAR: So there's a sort of a disconnect about what's been going on in reality.

MS. YOST: I don't think so.

DR. LLOYD-PURYEAR: No, really, because we used to support that lab. Ed can tell you.

DR. McCABE: Yes, the state laboratories, state public health laboratories, are somewhat outside this system, and we recognize that if you look at total number of genetic tests performed, 4 million is a large number. My guess is it's probably the largest number, but I don't know that, and so there's a significant area that's not being covered.

DR. LLOYD-PURYEAR: And my point being that this is -- I mean, please think carefully about the structures that you're going to be setting up, because this will affect those current newborn screening labs.

DR. McCABE: Reed?

DR. TUCKSON: I think there are a few people that want to get in on this point. You can get me in a couple.

DR. McCABE: Okay. Who wants to speak to this? Wylie?

DR. BURKE: I actually think what Dr. Feigal just outlined in terms of motivation to collect data upfront versus collecting data downstream is an absolutely crucial point. I know we've kept coming back to it. We really need to focus on it.

I personally am very comfortable with the idea that the data collection is in the hands of the developer proposing to put the test on and that there is some FDA process that looks at that data, and that our advisory input is just to make sure that the right kinds of data elements are asked. Perhaps look at what is routinely asked under FDA procedure and ask whether it addresses all the questions we would want

addressed for a genetic test.

But I think far more important is that we create a process that motivates and, in some cases, requires the ongoing data collection, and here I think there is a process that should be part of the initial approval. The initial approval is presumably for a defined and often limited indication. If a test has certain characteristics, and the obvious ones would be a predictive test where there are not proven interventions, it may be crucially important to have that second phase of data collection, because we'll never really understand the predictive nature, particularly of an incompletely penetrant trait, unless we collect that data.

In other words, we'll never get to the point of really knowing how the test should be used without that data collection, whereas there may be other tests that are diagnostic tests for well-defined conditions where that's less crucial. In the sense of conserving resources, I think a decision could be made that's sparing in that case, but the point is that decision can be made at the point of high motivation. You've got someone who wants to put a test online.

What I think is a much more crucial question is what's the mechanism for ongoing data collection and who pays what? I mean, it may be very reasonable for a person who is providing a test to kick back some money. In other words, to part of the fee being contributed to an ongoing data collection, but it seems like there's a public issue here that has to be thought through in terms of what's the responsibility of federal agencies to participate in that data collection and ensure that it goes the way we want to.

DR. McCABE: Reed?

DR. TUCKSON: Yes, I think that's where I'm at as well, and I'm impressed again that you have reminded us as to the ultimate purpose of all this, to what end all this stuff, and that is, again, our charge is to be able to protect the public and make sure that folk are treated right in this new era, and I think we've got to keep in mind what we're trying to accomplish.

But I am very concerned for Elliott and his industry and others who are going to have what looks like a redundancy of requirements, and I think that one of the challenges is that we have to be able to write our recommendations in such a way that CLIA's data collection and what is does has got to be a specific set of the data that FDA has to have, so it's all of a whole, so that people are not out here responding to all this doggone governmental regulation which stifles the whole universe.

So I think you've got to be very careful here. On the other hand, you've got to have it, so I think that we should be responsible, because if you want people to participate, you've got to be sensitive to the real world.

So I guess what I'm asking for, and I don't think we can do it today in the hour that's left, but somehow the CLIA folk have got to connect the data sets that they do to what we're asking FDA to do.

MS. BARR: And what CDC will want.

DR. TUCKSON: And to what the CDC is going to want, and that we begin to see all that of a whole, and since we can't define it today, I think the report has to say that's what we want to see occur and that there'll be an ongoing mechanism that we'll get back to later.

DR. McCABE: I think that's an important point that ought to be captured, that we really do need to look at how these current activities can be coordinated optimally. Again, I'm struck by the fact that the current system deals with tests and with laboratories, but it leaves out that clinical connection to the patient, both on the front end and the back end.

I have Pat Charache, Judy, Elliott, and Pat Barr.

DR. CHARACHE: The reason for my abstention is because I think it's important that all these tests be reviewed by somebody other than the developer before they go out, or else I would never have voted against it, but I'm concerned about three things in voting for it that I think have to be addressed.

The first is just the sheer volume. If we're talking about the home brews -- and that's what concerns me, because the rest is being covered -- in terms of test evaluation, each laboratory that uses a different master mix has got to be reviewed. We are really talking about thousands and thousands of tests. I'm concerned about grinding everything to a halt or, alternatively, having a stamp that goes through at the rate of 300 a day, and I think that's the worst possible outcome.

I think the other thing that concerns me very much about having it all in FDA hands without having modification of charge and resources is the off-label limitations, which Congress says they can't look at. I think that's going to be a huge part of this, where somebody licenses the test for diagnostics and uses it for predictives, and nobody has the authority to look into it.

So I think these two issues have to be addressed as we go forward.

DR. McCABE: We've talked about those for the last day and a half. I think everybody is concerned about those issues, and again, I'm seeing heads shaking, so those are issues that we ought to capture as recommendations that these are significant concerns. So we can get that off of the tape and put that in.

Judy?

DR. LEWIS: I think it's very difficult for us to sit in this room and think that we have the ability to recreate the federal agencies and recreate their charges because it's a pretty complicated system. So I think what we have to do is look at what's there that we can use and that works, and then develop programs for what's missing, and maybe the FDA can do a really good job on that initial review and the ongoing oversight CLIA can do with some modifications. So maybe there are ways to look at what's there and then look at what's needed.

Another model, when you were talking about the patient, one of the models that strikes me as one that's out there is the SART model, which is all of the assistive reproductive technologies, where clinics have to do an annual report of what their success rates are and use the same language so you can compare apples to apples, in a way. That's a professional association-driven model. So maybe there are some other models out there.

PARTICIPANT: What is SART?

DR. LEWIS: It's the Society for Assistive Reproductive Technology.

Maybe there are some other models -- and I mean, that's not a perfect one either, but maybe there are some other models out there we can look at, but to try to redefine the roles of the federal agencies that takes legislation I think is a little beyond what we can do in the next hour.

DR. McCABE: No, I think what we're recommending, though, is that the federal agencies need the resources, that this is a significant area and a growing area, and that the federal agencies need the resources to address their current statutory authority. They are stressed beyond the ability to do that.

The other thing I'd like to put out on the floor, and I've sort of been skirting around it, but Muin had to leave. Muin's piece really has to do with connecting the patient. So Muin had made a motion. I basically told him it was out of order, but we have that motion. If someone who's here would like to make that motion, we can recapture it from the tape in terms of Muin and then move on.

Am I hearing a motion?

DR. LLOYD-PURYEAR: He asked me to make a motion.

DR. McCABE: Okay. Can you remind us what the motion is?

DR. LLOYD-PURYEAR: Well, to create a workgroup between, I guess, the federal agencies first -- I mean, that's essentially what we already have -- to look at the issue of how to go forward with long-term effective data collection.

DR. McCABE: Well, I would put it more in a proposal to the Secretary or the Surgeon General, so that we feel there is this need, that in the current structure there is authority over tests and authority over laboratories, but that the ongoing data collection regarding the clinical efficacy of these tests, the clinical utility, clinical efficacy of these tests, is a piece that's not covered currently, and that we recommend that a mechanism be developed or utilized, if it's the current workgroup, in order to carry this forward.

DR. LLOYD-PURYEAR: So it's more in order to continue to evaluate tests as they're released into clinical work, we need this mechanism.

MS. BARR: My understanding was that our standard for getting it out was going to be far easier to reach, and that was that it had a specific purpose for a specific population and there was a connection, that our goal was that, given that, that as we wanted to expand and the label got broader, that there was going to be a data collection methodology, and that this is what this motion addresses, that this data collection methodology has to be created.

Is that correct?

DR. McCABE: Yes.

Do I have a second for the motion?

DR. BURKE: Second.

DR. McCABE: Okay. Further discussion? So is there a discussion, Francis?

DR. COLLINS: Just to clarify, this motion is not suggesting that a particular format be identified to solve this problem, only that it needs to be solved.

Is that right?

DR. LLOYD-PURYEAR: Well, but it also needs to be a part of the continued expansion of a test into clinical practice, that you need some way of collecting data to justify --

DR. COLLINS: But we're not identifying a specific body that would do that, only to say that a body needs to be found.

DR. LLOYD-PURYEAR: Yes.

DR. COLLINS: All right.

DR. McCABE: I had some other comments. I don't know if they're relevant to this discussion, but Elliott?

MR. HILLBACK: I was going to go back to the previous discussion.

DR. McCABE: Pat, do you have specific -- okay. Other discussion regarding this motion? Judy?

DR. LEWIS: I think what we're describing is part of the ongoing oversight process.

DR. McCABE: Yes.

DR. LEWIS: That the data collection is part of the ongoing oversight process. Just to put it in the perspective of the motion that we passed, which was what was available for -- you know, to get a test on the market, but that part of the oversight process, which I presume will be like a so- many-year accreditation process, the tests get revisited on a regular basis, and that this data collection piece be a part of the oversight process.

DR. McCABE: Wylie?

DR. BURKE: I think also what this motion is capturing, if I'm understanding it correctly, is this is a crucial part of the process and it's not immediately obvious how best to solve it, and so there needs to be a workgroup.

I think, to the extent that we're proposing we continue our advisory capacity, this workgroup perhaps is appropriately going to report to us about what the strategies are and have an ultimate decision occur here, although I didn't hear that as part of the motion.

DR. McCABE: Who established -- I mean, that workgroup was established before us, so the concept -- I mean, if there's a reporting relationship, it's going to be a dotted line relationship. But certainly, I think this group would like to be apprised of the progress there.

Michele?

DR. LLOYD-PURYEAR: The Public Health Service has an interagency group on -- what?

PARTICIPANT: (Inaudible.)

DR. LLOYD-PURYEAR: Oh. Well, I still think I'm part of the Public Health Service.

Anyway, they have a Genetic Testing Workgroup, and out of that there was a charge to form this smaller workgroup on data collection, which is actually all the same people here, all the same federal agencies.

But I mean, the thing I think that needs to be emphasized is that if in fact we want a streamlined process of getting tests out into the marketplace, this is part, and a necessary part, of that streamlined process, and I would emphasize that. It's not to put up a roadblock. It's to help streamline the process.

DR. McCABE: Because, again, I hear a lot of the same things over and over, does anyone wish to speak against the motion that's on the floor? Reed?

DR. TUCKSON: I'm sorry to slow us down, but can I just have the motion reread, please?

MS. CARR: Michele, do you want to do it?

DR. LLOYD-PURYEAR: No.

MS. CARR: I think the motion is that a critical part of the ongoing oversight process is the collection of data, and that this committee endorses the development of a mechanism to establish some kind of ongoing data collection effort.

DR. McCABE: Is that -- okay.

Pat?

MS. BARR: I just want to raise an issue, and perhaps it doesn't fit here, but it seems to me the FDA has already said, boy, handling first time around with these tests is going to be enormous, but we'll try and figure out a way to make this expedited and doable. Perhaps we're the right organization. I don't think we've resolved that.

But then to add to their burden, are we presuming that that's going to fall under their rubric or are we not presuming? We're making no presumption. Okay. Then I'm comfortable.

DR. McCABE: David?

DR. FEIGAL: Well, I'll be curious who you think would enforce it, but I think that one of the things to remember about the therapeutic approvals is that the logic is that if you approve something for an indication and the manufacturer never wants to claim anything new about it and still manufactures it in the same way, that if nothing new is learned about the product, that it can have that indication indefinitely.

There actually are more device authorities to require post-marketing studies and follow-ups, so FDA does

have that authority. Usually, almost always, it's in the setting of the safety of the test requires this, and so that would have to be the logic of doing that, and I think you'd have to make the case probably test by test where it made sense to do that and where it didn't, but the only authority the agency would have would be on the manufacturer to require that.

But you're setting it to imply that ongoing oversight, collecting more data, requires it. Just like the comparative standard, that's setting a higher standard for these tests, so I think this is one of these things where it's hard at the same time to talk about not wanting to hold this field back, and at the same time holding a higher standard to this field than you are to development of other new diagnostics.

DR. McCABE: I think the issue, though, from the discussion that we've been having, is that genetics is a little bit different, that if you approve a test for sodium, then you're going to be able to measure sodium, but if you approve a test for a genetic test in a specific population for a diagnostic test, that once that's on the market, to now approve it for the whole population as a screening test, it's a very different test. So, that's part of what we're dealing with here, I think.

Wylie?

DR. BURKE: I actually think that what we're proposing fits into that rubric fairly well. So I could easily imagine that if you're proposing a new, improved test for the sickle mutation, there wouldn't necessarily be much interest in ongoing data collection, and that would be the limited indication for which it would be used and it fits into that rubric.

I think actually if you're bringing a predictive test to market, particularly a low penetrant predictive test that has enough clinical data for people to agree that it's probably worth providing, nevertheless that could be exactly like the device that more safety data is needed for. I think safety is a reasonable argument there.

So I think we need to hear from the working group, assuming that we have a working group. In other words, I think it is precisely those kinds of issues that need to be considered in parallel with practical plans for data collection and analysis. That is, what kinds of data, for what kinds of test, to what extent would there be regulatory authority behind them.

DR. McCABE: I have Pat Barr, Elliott, and then Reed.

MS. BARR: I guess I had another question, and that is, CLIA, because there are so many labs, has set up a system of deemed approvers. Is there a mechanism within FDA, where we're looking at genetic tests, where there could be relationships with professional organizations to be deemed reviewers that would facilitate the more straightforward reviews that we want to have?

Because I think our concern that Elliott was so upset that we had was just that there should be an independent review, that that data that he's relying on, the clinical research that he's relying on, and then he does his test, is good and is right, and that should be a pretty straightforward process, but it could get very bogged down unless there is some mechanism for creating these other reviewers.

DR. McCABE: David, could you respond to that, please?

DR. FEIGAL: We also use the states, for example, in some of our inspectional and review processes. We also have the authority to have third-party reviews and we can contract.

The only thing is that the person who's doing the review for us has to meet the same standards that we do in terms of conflict of interest and produce the same kind of product that we do, but there's no requirement that we do the work ourselves. It can be an extension of us.

DR. McCABE: So should we capture that also for the report? Because I think that's a very important point, that in order to accelerate the process, that we would encourage FDA to seek partners that would meet their standards, but that could be given deemed status so as to move products and tests forward.

Is that a fair --

MS. BARR: Yes.

DR. McCABE: Okay. I don't think we need to vote on that unless anybody -- is there any disagreement with that?

DR. BOUGHMAN: No disagreement, but I would point out that this body is also advisory to the Secretary, and that maybe you may have just made a very large resource statement about volume of tests and the ability, given personnel and budgets and so on, to handle that without making sure the Secretary understands that there might be a difference.

DR. McCABE: Yes, I think that what we were trying to do was encourage exploration and not say it must be done. If people feel it's significant enough, then we can vote upon it, but I don't see anybody disagreeing with it.

Reed?

DR. TUCKSON: I guess where I am on this is that I'm really anxious about the implications of all this without having the opportunity for us to be specific. To grant deemed status, I just don't know what that ultimately will mean in terms of the overall health delivery system.

I think that, if I understand where we are, we're talking about the creation of a committee, which assumes, by the way, the data for the rest of this chart, not just the little part that we're on. So I think that if I understand, which we have not stated explicitly, that the kind of data committee we're talking about will be ultimately charged with the whole dang chart. We're just at the very top of it.

And in that regard, then, and given the lateness of the hour, Francis made a comment and others have agreed with him that we really cannot now speak in any level of detail to what this committee will do, only using it as a placeholder and recognizing at some point that we will have to get back to charging the committee and defining it.

I can live with -- because we got into this whether we would all agree to this amendment or not, I mean this vote -- I can vote in favor of it if it is as bland and neutral as that, but I think that the writer is going to have to be very sharp at crafting the kinds of supplementary discussion that we've had so people get a sense of what we mean and what we don't mean.

I would think that, at the end of the day and in conclusion, that I would hope that we would have an opportunity before this thing is put to bed in two weeks perhaps to develop a charge, and if not, then we simply have to have some kind of language that lets people know that this really is as neutral a statement as it is and that we will get back in later iterations of this committee's life to being more specific.

But I tell you, this is a terrifying area and people will read into it all manner of stuff, and we need to be very, very cautious here.

DR. McCABE: Elliott?

MR. HILLBACK: Yes, I guess I'd like to kind of go back a little bit so I can come forward.

I understand it was very easy to take a vote to say, yes, someone from the outside should look at every test before it goes into clinical practice. I think the reality of that is virtually no hospital that's doing a DNA test will keep doing one because they have no resources to do that. Most other DNA tests don't have enough volume to justify the cost of going through FDA.

And I would ask David if you get into situations -- if we assume that FDA is the gatekeeper for every test and that the CLIA process and other processes are not, how do they reconcile safety and efficacy with a predictive test where we now have some clue that this mutation may be predictive, you know, to a certain level, but it's still very early in its development, and how does the FDA in its safety and efficacy, in this package that we were all given, how do we reconcile that?

I think we've taken a major step in really reducing the availability of genetic information if we follow this all the way through. My concern about doing that was to take such a vote without thinking about is it FDA, is it CLIA, is it someone else, is it some other mechanism? Unless we get into those details, I think we made some assumptions that the system can cope, and I don't think the system can. I think we've made a very major vote towards basically stopping.

But I'd like to hear David's response. I'm sorry. I'm not trying to pick on him, but I don't know how to do it.

DR. McCABE: David, then Wylie and Francis, and then we're going to move on to the threshold issues.

DR. FEIGAL: I guess I interpreted the vote of the outside party to also include IRBs, local IRBs, and the question in my mind, and maybe I misunderstood the vote, because if you have voted for that, then you're essentially saying that all genetic tests have to be under investigational device exemptions, because you can't come for an approval when you start a new test because you haven't gotten any data yet, right? So if you're going to start a test and it's investigational, then in fact you need to have an IDE for it, and that's currently not the standard.

I think the broader, sort of philosophical question is sort of what is the role of that IRB oversight and informed consent for new diagnostic tests that are developed in a single laboratory? I'm sure that some of them do use informed consent. Some of them may not.

MR. HILLBACK: Let's come back to even simplify it, because we talked about this a little bit earlier. Let's assume that a paper gets published out of one of the major research institutions that says we've

drawn a correlation between this mutation and there's some predictive value to this mutation. So 10 labs, the major labs -- Mayo, Baylor, Genzyme, Roche, whatever -- say that's great. There's this peer-reviewed paper and we want to develop a test.

Now, what would we do from there to get through FDA to be able to put a test in the market?

DR. FEIGAL: Well, the short answer to that is that you have to have actually studied your test. So you can't just bring it to the market without having used your test. You can't say I've never done this test before, but I'd like to bring it to market. So there has to be a period of time where it's an investigational test, and that's how you're going to establish the performance of you doing it in your individual laboratory, since each of these 10 places has decided to become its own manufacturer.

MR. HILLBACK: So if I can prove that I can find that mutation 100 percent of the time in the dark with 10 different technicians, absolutely find it every time -- so I've found the mutation, but I've never gone any further to go out and follow patients for a period of time to see what their outcomes are, is that fileable on that basis?

DR. FEIGAL: Well, if the literature established the relevance of the test, then that would in many circumstances be adequate. The laboratory would not have to independently do that. They would just have to say the literature established the relevance of this gene, I can show you I can find this gene accurately, and that would be sort of the gist of an application with the manufacturing details and all that type of stuff.

But the step before in my mind is it's going to require actually performing the test in some clinical kinds of settings, and that's what is probably going on with a lot of tests right now, is that people are evaluating some of them.

MR. HILLBACK: But that's probably not being done in a clinical setting by any of the labs that will eventually do the test in any volume. That's done in a research facility by people who are trying to treat the disease or study the disease.

So take Gaucher's disease or Fabry or Pompe or any of the lysosomal disorders, we aren't doing the original research on the disease. That's being done at various hospitals around the country. They've developed a relationship between a gene and an outcome and publish a paper, and we look at that and say that's a test we could do and it's a test that there's a need for, and now we want to go from there. So we aren't really the researcher in that sense, and that's really the more realistic view of how new tests are coming to the market and will come to the market.

DR. FEIGAL: The main difficulty we have with research is that it's typically three pages long, and usually the editor has requested that the methods section be cut way back, and there is certain emphasis in the journals and things, so for us, our stock in trade is to actually review the primary data and the original data. This is an area where cooperation of the whole genetics community, of sharing the studies behind the research in more detail, not just with us, but also laboratories trying to understand the significance of that, would be very helpful.

But I think that, again, it all comes back to working backwards from what the claim is, and those situations where you're claiming that you found the gene, then it's much less burdensome than a situation

where it's very unclear what the gene means, and we have all this phenomenon in the literature where someone claims a strong relationship and over time it sort of gradually erodes for a variety of different reasons, and those are difficult situations.

DR. McCABE: Wylie and Francis had things to say on this.

DR. BURKE: Yes, I just want to follow up on that. I actually think a single peer-review journal is generally a very weak basis for bringing a test to market, and I think we have a lot of examples already where that's been done and it's proved to be a rather unfortunate kind of test to be using.

I would just go back to what I think was a somewhat nihilist remark. That is, if we require every test that comes to market to have some sort of external review, genetics is going to come to a grinding halt.

I think if we carried that to its extreme what we'd really be saying is we can't do it and therefore we should be bringing tests to market without review, and I think that's a very unacceptable position precisely because tests have been brought to market on the basis of peer-reviewed literature that in retrospect proved to be unwise tests for clinicians to be using.

So I think the emphasis has to be where we've been putting it. That is, trying to think very carefully about what is a reasonable, non-intrusive, reasonably limited process for bringing good data to the attention of whatever external body reviews it. I think when we say that every test needs to be reviewed, we are committing ourselves to a reasonable level of review, not overly intrusive and overly burdensome, but reasonable enough to ensure that we don't have those wacky tests that are based on a single peer-reviewed paper that says there's an association that turns out not to be there to come to market.

MR. HILLBACK: It's in no one's interest to do that.

DR. McCABE: Francis?

DR. COLLINS: Basically, I wanted to agree with Wylie's summation, and also to say I think, Elliott, your presentation was unnecessarily gloomy of the impact this would have. I mean, if you're particularly worried about tests that are already being done for which good validation exists, my sense would be those are circumstances where, yes, we should have some sort of review, but this idea of deeming, as Pat brought up, which I think is a very helpful kind of mechanism, those kinds of reviews to be done quickly by professional organizations, then simply it comes down to is this lab capable of analytical validity or not, in which case it's a CLIA issue. I don't see this as sort of ending genetic testing as we know it, which is the way you made it sound.

DR. McCABE: Okay. I'm going to now take the chair's prerogative and move us along, and we really need to start dealing with the issues, and I think that will let us deal with thresholds and some of the other things.

First, Issue 1, and this is under Tab 2, is the summary, but I think we've already embellished some of these things, and I'm going to suggest some structure or at least some of the components that we've already discussed.

Under Issue 1, what criteria should be used to assess the benefits and risks of genetic tests? We talk about

this to some extent -- do you want to pass out those handouts? The staff has summarized these nicely, but if you look at some of the criteria under Issue 1, we've talked about clinical validity, clinical utility, the social issues that are raised.

I think, again, under that then this morning we talked about the three axes, and that certainly we knew where there were higher concerns and lesser concerns. We had some lists that we talked about criteria for review that had to do with frequency. Again, this will have to do with the benefits and risks criteria because, if we think through these, these involve benefits and risks. The frequency, screening versus individual testing -- the bullets that we had from this morning. Potential for stigmatization of individuals and/or populations, the health relatedness, the availability of independent methods of confirmation.

So I would suggest that we've really dealt with Issue 1, both in our previous deliberations, plus our extensive deliberations this morning, and is there anyone who feels that we've left out something significant?

Sarah?

MS. CARR: No, I don't think you left anything out, but I remember some discussion about severity of illness, and that that might not be an appropriate factor as I think it's a factor in your current discussion, so would you actually take that out of consideration? You didn't have it in here, but it's in -- pardon?

DR. KOENIG: I was going to say, part of the issue is severity according to whom?

MS. CARR: It's subjective. So should that come out of the --

DR. McCABE: So you're saying it's in this document.

MS. CARR: It's in the current discussion under I think utility. The nature of health condition and health outcomes discusses severity.

DR. BURKE: There are two points here. One is I think we do need to modify our original approach. That is, I think we got useful feedback on that point about the subjective nature of evaluations of severity.

On the other hand, I think we have come at that in a different way when we talk about potential for stigmatization, and we may actually be dealing with the crucial piece. There's subjective evaluation there, too, but I think what we're saying is we want the oversight advisory capacity to include some direction about what are the red flags, basically, that increase the likelihood for stigmatization. I think that probably captures that portion of "severity" that may be most important to us.

DR. McCABE: Wylie, since no good deed goes unrewarded, I would ask that you look over this section with respect to our discussions as well, and Pat Barr perhaps, too.

PARTICIPANT: So should --

DR. McCABE: Yes, if the three of you would really work on that, and there'll be other people, other assignments made. But also, in terms of the draft, everybody will look over the whole draft, but if you could really focus on that.

Other important issues? Pat, and then Judy.

DR. CHARACHE: Just one thought, which came up with something David Feigal said a moment ago. Some companies will say that the purpose of their test is to detect a certain gene modification, and I would say that that's not adequate information, and I think that that should be made very clear that that can't be the purpose of the test.

DR. McCABE: And I think we've discussed that some, but it's important to reiterate it.

Judy?

DR. LEWIS: I think the issue of living with -- I mean, the issue that we need to deal with that I heard, but not necessarily on the table as much, was the whole idea of what it means to live with a genetic illness, and then when we get the technology, to be able to do prenatal diagnosis. I think that's a big, big black hole, and I think we need to be careful how we deal with that issue.

DR. McCABE: Let's move on to Item 2. Item 2, or Issue 2, has to do with this issue of high risk, low risk, and I think again this deals with the axes, but now is where we need to look at some of the threshold issues as well. I think they probably fit in best here.

So we've talked about risk, but that risk becomes particularly important at the area where you cross from a research to a clinical test. So in the context of the risk, let's also look at what are our thresholds? What are going to be reasons why we consider something higher risk and we may give it more close scrutiny?

Yes, Pat?

MS. BARR: Well, I would think we would put common diseases, late onset, so that these become predictive tests, in a higher scrutiny box, because in order to understand their predictive value over time, we will need time and we will need a significant amount of data. So the threshold for that to be out for the public broadly needs to be a much higher one.

DR. LEWIS: And I would add to that the piece of tests where we have little or no prevention strategy, so not only is it the predictive test, but the test in which we don't know of any modification to alter the outcome.

DR. McCABE: So again, we're talking about that continuum, and we certainly knew on two of the axes what was the highest risk. There was the third axis, which had to do with the penetrance, where there was some debate on that.

Wylie, you want to pursue this?

DR. BURKE: Well, actually, I want to say two things. The first is that I think we got feedback that I think was useful in terms of wording or semantics, and that is we may be better off saying high complexity, low complexity, and maybe, even following what Pat just said, we're really talking about high scrutiny, low scrutiny. I don't know if that's the right way to say it. Complexity is a little bit more neutral.

I think we've actually already discussed this fairly well. I mean, I think if we go back to the two lists we made, one was the axes and the other was sort of points --

PARTICIPANT: Criteria for review.

DR. BURKE: Criteria for review. I think we've got those.

DR. McCABE: Right. I think that actually Issue 1 sets those. Issue 2 begins to rate them. I think this section is going to change substantially from what we had in our preliminary draft. Or it wasn't a draft, but just our thoughts, our discussion.

So who would volunteer to review this?

Kathi is going to capture the discussion, look at what we have been talking about, because I think you're right. We have discussed this extensively.

Can I have some volunteers for looking at Issue 2?

PARTICIPANT: (Inaudible.)

DR. McCABE: Yes, I think that we can separate them. It's a somewhat artificial separation, where you set the criteria in 1, you evaluate them in 2, but I think that because they are so similar, maybe the same group could look at 1 and 2.

Judy, do you want to --

DR. LEWIS: I'm asking to join that group.

DR. McCABE: Okay. Anybody else? Okay, Mary. So Mary and Judy are added to that group to help look at both 1 and 2.

Number 3, and as you're going through this, look at the subquestions, too, but we've dealt with those in the public comment and I really think that, as I look at them, we've covered them in our discussion, the Subquestions 2.1 and 2.2.

Issue 3. What process should be used to collect, evaluate, and disseminate data on single tests or groups of tests in each category?

So if you look at Issue 3, then, who collects the data, and I think we've reiterated that for the things where there is already statutory authority, that those agencies should continue to collect and evaluate those data according to their mandate, that we have to recognize that there are issues about genetic testing that may cause a different type of review, and we've also discussed that there may be ability to bring in other groups, other professional groups, that would meet standards but get deemed status with the goal to increase the flow and not have the bottleneck.

There was discussion about modeling after tumor registries. We've heard lots of models.

Do you want to discuss that, Wylie?

DR. BURKE: Well, I just want to comment that I think this is where the message we need to communicate is what we've just discussed about creating a working group. In other words, I think the where we are in this is that other the kind of data collection that we already have clearly established precedent and regulatory authority for in different agencies, there is a component of data collection and analysis that we've identified that we see as important to genetic tests, but we're not certain at this point what's the best mechanism to accomplish that, and we're recommending that a working group address this and report back. I think actually to try and get to more detail would be inappropriate. It would be undercutting what we want the workgroup to do.

DR. McCABE: I think, though, that there are some things that were in our original thoughts, and that had to do with dissemination to the public and to the health care providers. We need to be sure we capture that.

One of the things that Sarah reminds me, and Becky reminded her, is that we never voted on the motion about the workgroup. A minor detail.

So do you wish to restate? Do we have that motion?

MS. CARR: That was the one I made the effort to.

DR. McCABE: Okay. So we've already heard it and it's been seconded. We had discussion. In fact, we had moved off that discussion.

So all in favor of that motion, please raise your hands. Up high, please. This is a roll call vote.

(Show of hands.)

DR. McCABE: Okay. Any opposed?

(No response.)

DR. McCABE: Any abstentions?

(No response.)

MS. LAWSON: Twelve, zero, zero.

DR. McCABE: Other discussion on this Issue 3? Because it had not been fleshed out before, but I think really our discussion has informed us, and again we can trust Kathi to capture it.

I need some people who will look at this, though.

DR. TUCKSON: I will.

DR. McCABE: Okay, Reed.

PARTICIPANT: What about Muin?

DR. McCABE: Yes, Muin. Michele, Elliott. Judy, did you have -- yes. Mary, David, and Steve Gutman. Is that okay with you? Okay. Thank you. So that'll be a large group, but it is a large task because there wasn't much there before.

Issue Number 4. Oversight of genetic tests. This one I want to be sure that we're comfortable and that we all understand what it is that we're talking about.

We've talked about current oversight. There was a discussion of introduction of laboratory-developed tests and we just discussed that yet again.

Patient safeguards. Let's just talk about patient safeguards a little bit. Are we satisfied that these are adequately covered by the current mechanisms if, in addition, we begin to explore or we have this workgroup that's exploring data collection? Because I think we need some connection from the laboratory and the test to the patient.

Pat.

MS. BARR: Well, it seems to me here we should talk about labeling and public disclosure of labels. We might want to look at a centralized place on a Web site that has genetic tests and then talks about what they're approved for at any given particular time or what we know they're useful for at any particular time. I think that that would be very useful for the public and for the clinicians.

DR. McCABE: Under here, we had information disclosure/marketing, so what you're saying is we need to also discuss the need for developing appropriate labeling as part of that disclosure.

Pat Charache?

DR. CHARACHE: In the area of informed consent, I think there is a need to have some strategy for prioritization, for saying which tests require it and which ones do not in the patient care period.

DR. McCABE: Yes, in the research phase, I think it was a motion, we discussed the need that all tests be reviewed by an IRB during the research phase. So now we're talking about the clinical phase, and Wylie, you want to discuss this?

DR. BURKE: Is it reasonable that as we create a template for that initial review that we give test developers criteria of the kind of test that we would normally consider to require a signed informed consent in clinical practice and ask them to identify and explain why their test does or does not fit into that category?

I think if we could create the right kind of template, simply explaining very clearly what tests do and what tests don't, it's fairly simple for a test developer to figure out which box they're in, and it doesn't slow down review in any way. It's just a yes or no.

Is that reasonable?

DR. CHARACHE: I think that's very reasonable. I think there will be other factors in terms of how it's accomplished and who keeps it and how it's monitored.

DR. KOENIG: I just don't want to move off the issue of the communicating to the public. We had some suggestions about Web sites in, but really the one issue was the issue of at this point do we suggest actual mechanisms for oversight of the way in which things are communicated, especially in terms of direct to consumer, or do we just suggest a mechanism for dealing with that later? And I just don't want to leave that without being clear about what we're doing.

DR. McCABE: There are a couple of issues that came out of the public comment that we do need to address. We're going to need to break in just a few minutes, too, but one was the direct to consumer. The other was the orphans and what is done with them.

So how do people want to address this? Yes, Judy, and then Pat.

DR. LEWIS: I think there are two groups of consumers, and one are the people who order the tests and one are the patients who use the tests. So when we talk about the information and the education and marketing issues, I think we need to look at both groups, because we've got a whole bunch of providers. As this becomes a part of general care, as opposed to a part of referral care, we've got more and more providers, and we're going to get into the 4 million babies, but we're going to have the 2.2 whatever we are number of Americans who are going to become the potential patients, and all of the health care providers out there. So I want to make sure that we capture the piece of making sure that we're doing it to both groups adequately, because it's going to become not a referral practice, but a part of general practice.

DR. McCABE: Pat?

DR. CHARACHE: I think we've addressed the orphan test when we talk about the requirements for accuracy and information that's needed, and I think that also, as Wylie said before, comes into the implementation and what the levels of criteria are considered satisfactory.

DR. McCABE: Okay. Why don't we take a 15-minute break. We'll resume at 3:15 sharply, so please be back in room because we need a quorum.

(Recess.)

DR. McCABE: If everyone who's in the room will take your seats, we've got a quorum, as I count, anyway.

We really aren't finished 4. There were some people who had to make some phone calls, so that's why we broke when we did, but have we talked about post-market data collection? I mean, that was that thing that we talked about.

One thing that Reed said that we need to be sure to capture in that is that the purpose of that is not to burden either the medical establishment or the federal bureaucracy, but it's to help make the connection with the patients, and that it's a very focused data collection and not a very broad data collection. He's on that group, so I think he can help capture that, and he's particularly sensitive to those issues.

Yes, Barbara?

DR. KOENIG: Sorry to add anything, but is this the point -- since one of the main issues that the public raised is in this category, do we need to say anything more specific about the protecting of the privacy of this data? Suggest mechanisms or --

DR. McCABE: Well, we're going to put up in the very front the issues about discrimination, the risk of stigmatization, those sorts of issues. Certainly, it doesn't hurt to say things more than once, so we can certainly put privacy and confidentiality in here and refer to some of the problems associated with breach of those.

MS. BARR: I think we could also say that it makes it difficult for us to recommend the ongoing data collection which is necessary for broad use of tests if those protections don't exist.

DR. McCABE: One of the students quoted Dr. Collins on page 757 of here. I had made note of it because I thought it was a quote. Ashley Lester from Rome, Georgia, and I assume this must be on a Web site or something.

"Genetic information is highly personal and unique. The potential for its misuse threatens to penetrate many aspects of life. However," 'The American people will receive the full medical benefit of genetic testing for predisposition to illness only when genetic discrimination barriers are lifted.' End of quote, parens, Francis Collins, director of the National Center for Human Genome Research.

That's an old quote, I guess, Francis.

I think it might be nice to take that paragraph almost, because I think it really captures it very nicely. Again, these were incredible responses that we got.

Is that a reasonable thing to --

MS. BARR: But everyone knows Francis will say that, so I think it's very important that we say it.

DR. McCABE: Well, but that's why I thought it's even more important that we attribute it to Ashley Lester saying it.

Data disclosure. We had some discussion in our previous document about no current requirement the data about a test's analytical validity, clinical validity, or clinical utility or lack thereof be disclosed to health care providers. We've talked about that and that will be covered under labeling, I think, and so we've made some recommendations there.

Promotion and marketing. Anybody want to modify what we have said there? Pat.

MS. BARR: I just would like to add something on orphan diseases. Here I think that direct marketing or direct information to the patients through a Web site mechanism that would help an individual review their symptoms and the appropriateness of a test could be very helpful since so few physicians can keep up with or can really understand the range of orphan diseases, but individuals with symptoms are really looking for an explanation of what's going on.

So it seems to me, as we think about the Web as tool, that that might be an appropriate -- we should think about how to use it for orphan diseases.

DR. McCABE: There is GeneTest, which provides some of those information.

PARTICIPANT: Do they provide it on orphan diseases?

DR. McCABE: Well, no, GeneTest doesn't do it on orphan diseases per se, but certainly most of the diseases that are there are orphan diseases. I was looking through it in preparation for this meeting, and I was struck that they have those that are available for service, those that are available only for research, and I think that as I looked through it, it looked like a pretty reasonable list, though again it might be a list that some group might want to look through in more detail in the future.

Francis, did you want to say something about that?

DR. COLLINS: Only to say I think it's also advantageous, because it is set up by an objective sort of central clearinghouse, and so with regards to Pat's comment, which I agree is really important, it's one more step to make it possible for an orphan test to be presented in a fashion that has had some kind of review.

DR. McCABE: Sarah's suggesting that one of the things that we might suggest, in keeping with your concern about orphan diseases, is that we might suggest that there be a look -- and Bonnie Pagan is the P.I. on that. Is it covered under an ELSI grant?

DR. COLLINS: It's jointly funded by Genome and the National Library of Medicine, so it's actually a National Library of Medicine grant.

DR. McCABE: Would it be appropriate for us to recognize the existence of this resource, but also suggest that they should look at the orphan disease implication? You know, they should particularly look at orphan diseases.

Wylie?

DR. BURKE: I actually think both GeneTests and GeneClinics, that it would be appropriate for us to acknowledge, and they're both publicly supported databases, but if we do, we may want to note that they don't at this point incorporate a systematic review of evidence that rates quality of evidence, a la the model of the U.S. Preventive Services Task Force, which is not to say that they aren't probably the best resources we have. Only to say that as we get better at this data analysis and collection process, the data in those resources can be improved. At least we can acknowledge and inform people about quality of data.

MS. CARR: Wylie, do you know how they prioritize? At GeneClinics, in particular, how do they decide on what diseases they're going to present information about? Is there any priority given to orphan diseases?

DR. BURKE: Not that I'm aware of, but Bonnie would have to be queried about that. I know that they have an editorial board and I'm sure that's a point of discussion, but I don't know whether orphan diseases

has come up as an issue.

DR. McCABE: Well, I don't think that we can specify what's in the grant, but I think that we can encourage that this is an important issue, that the quality of the evidence needs to be looked at, and this seems like a group that would be appropriate to do that. But again, we can't specify that.

Wylie?

DR. BURKE: I'm sorry. Just to amend, because I think it's probably the politic way. I don't think we should question the quality of the evidence they put on. I think they provide as good evidence as there is, but we might want to note that they don't rank the quality of the evidence, and that their dissemination of information would be of greater value to the extent that they could rank the quality of the evidence behind each point.

DR. McCABE: Pat, and then Victor.

MS. BARR: I have one other orphan disease issue. It came up in the task force and I don't know if we've dealt with it here, but that is that often these are a single laboratory, a single investigator. When the investigator wants to stop doing this, we need some mechanism to be sure that those tests remain available.

I think that's an oversight in responsibility, in fact. Otherwise, we're going to lose a base of knowledge, and just as we're talking about building a base of knowledge, I think we have a responsibility to find a way to keep the ones we have.

DR. McCABE: Victor?

DR. PENCHASZADEH: I just wanted to comment that there are a couple of letters from Bonnie Pagan offering to make herself and GeneTests and GeneClinics available.

DR. McCABE: Yes, Barbara?

DR. KOENIG: I still feel we're losing the non-orphan disease marketing issues. What about the issue of promotional and marketing materials for possible tests that affect, say, half the population? And what do we want to say, if anything, about those kinds of issues in terms of whether they need some kind of review prior to being brought to the public's attention in some form?

DR. McCABE: David, do you want to tell us what the current rules are about this in terms of direct marketing in general?

DR. FEIGAL: There are two settings. One is where you are doing what are sometimes referred to as "reminder advertisements," where you're informing the public that a product exists, ask your doctor about it. You'll see that for various -- antihistamines do it, Viagra's had a campaign for that, although I can't imagine they need to advertise. But anyway, those are reminder ads for prescription products.

The other category is where a product is approved for over-the-counter use, and then there's a whole series of -- first, you have to establish the product can be used over the counter, and then the marketing is

direct to the consumer because that's who's using the products. That wouldn't really apply in this setting very much. Here it would be the kind of advertising that would probably be more in the reminder-type category.

That is reviewed by us. Advertising is complicated because it's a split responsibility between the FDA and the Federal Trade Commission. Sometimes they have jurisdiction, sometimes we do.

DR. McCABE: Barbara, did you want to follow up on that?

DR. KOENIG: I just want to follow up and say that the ads that I have in mind that I'm concerned about are the direct-to-consumer reminder ads for BRCA1 and 2 testing that are currently out there.

DR. McCABE: So do we want to include that this is an area of concern for us?

Joann, can you help us?

DR. BOUGHMAN: It's even an area of much greater concern as reported by the public, because there were differences of opinion, and we may have an in-between situation here where the test is actually performed by the laboratory, but the question is can that be requested directly and performed directly for the consumer? Not over the counter, but by a certified laboratory without the intervention of a licensed professional. In other words, can I go to a lab and ask for the test myself?

This is an area, at least from my perspective and my experience on FDA panels, that is not an area that's been addressed before and we are going to have to look at that one carefully.

DR. McCABE: Any other thoughts on this?

MS. BEARDSLEY: Yes, it seems to me that one thing we might do -- I don't know if we can make this kind of recommendation, but one thing we might think about is suggesting or asking FDA and FTC together -- and I understand that FTC's not subject to the jurisdiction of the HHS, but nevertheless, to take a look a little bit at what's out there, because I think that the enforcement jurisdiction exists. It's simply not being exercised.

DR. McCABE: So we will capture that as well, that we would like to pursue some discussions, and we could certainly invite someone to one of these meetings from the FTC.

MS. BEARDSLEY: I've talked to Jodie Bernstein, who is the person at the FTC who would run this, a little bit and I think she would be happy to talk to us.

DR. McCABE: Joann, did you have any follow-up on that before we move on?

DR. BOUGHMAN: I'm not sure. I'd like to ask the FDA if in fact there is a need or whether it's appropriate for this body as an oversight body to request some work on at least a guidance document on these tests that fall in-between the OTC and the prescription.

DR. FEIGAL: Well, yes, I think the problem you point out is true of all tests in the states that allow consumers to order tests for themselves without -- and then it becomes a little bit disingenuous for the

manufacturer to say, "Oh, I've just got professional labeling. Don't worry about it." So I think, yes, certainly we'd be happy to consider that.

The other area that is of great concern to us is what's going on on the Internet, partially by companies, but also by distributors and other kinds of third parties.

DR. McCABE: Thank you.

Victor?

DR. PENCHASZADEH: A related subject, and I don't know if this is a matter for now, but the question of the information that the performing labs offer for patients through the physician. I mean, most genetic labs would hand out descriptions of the tests that serve not only for the education of the clinicians, but primarily for the clinician to hand out to their patients. It's one of the common ways patients learn about the different types or characteristics of a particular test's limitations, possibilities, and so on.

Is that something that we should look into? Is there any authority that should look at the content of those descriptions?

DR. McCABE: What about package inserts? I mean, if one looks at -- and I don't know if that's considered formally an extension of labeling or not.

DR. FEIGAL: The package insert is part of the labeling, but for many devices the label doesn't even go to the person who ordered the test. It ends up in the clinical thologist's hand.

I think the other kinds of tools that are also part of labeling are labeling designed for health consumers and for lay consumers, and that's something that certainly should be addressed for these products.

DR. McCABE: Do you have any mechanism for any of your other testing -- you know, we're all familiar with the PDR, which is basically a compilation of package inserts. That's not done for other tests or is it done for other tests?

DR. FEIGAL: There really is not a comparable compendium for devices. Part of it is just the difference in the volume of devices compared to drugs. There are about 50 devices approved for every new drug approved, and so where the PDR might have labels of several thousand products, a comparable device document might need labels on hundreds of thousands of products. So it's just never been put together.

The PDR is actually paid advertising. It's put together and they pay for it by the -- and not every product is in there and the labels are not always the current labels, even when it's published, but it's a pretty good source.

DR. McCABE: But as we were talking about Web-based technology, would it be appropriate to request that labeling for these products be available to the public perhaps --

DR. FEIGAL: Well, one initiative that the Center for Drugs is undertaking because of the problem of keeping labels, which frequently change, up to date is a cooperative project with industry to have a Web-based compendium of current labels. It might be possible to try and pioneer something like this in this

area for diagnostics, since it's a controllable universe compared to all diagnostics.

DR. McCABE: I know that Judy has something to say, but I'd like to just be sure. Would this be something that people would be comfortable with as a recommendation?

Judy, do you have something to say on this?

DR. LEWIS: Yes, my concern with this is that if we're doing something that's going to be a consumer education piece, that I know sometimes I have trouble reading some of the package inserts, and I think the issue is that we have to have it at a level of, you know, sixth-grade readability in words that people can understand and have it have some relevance to consumers, and also have an opportunity to have it be available in more than just English. But I mean, to me the readability issue is a key issue.

DR. McCABE: We can certainly recommend that. The nice thing about the labeling issue is that it's covered under current regulatory authority, and we would just be suggesting that as this is developed that it be compiled, but I think we should also add your caveat that to the extent possible we explore mechanisms to get these so they're readable.

DR. LEWIS: Because I think the last thing we want to do is do something that's going to further mystify by putting out information that people can't understand, and I think that's a bigger disservice.

DR. TUCKSON: Do we have testimony that we can at least use on the question of health literacy and the public's difficulty already in understanding health issues? And then this on top of it is doubly difficult. If we got anything in any of our sessions on that, I would urge that we have a template for that earlier in the report.

DR. McCABE: Yes, I think that that was certainly a topic that many of the individuals commented upon, and we could have Susanne extract that. I think she's memorized those comments, so she could extract some key points.

We're going to talk about that, too, because I think to the extent possible, where we can identify commentary from the public, we should use that not just as an appendix, but actually in the document to support this, and I think this is another example of this.

DR. TUCKSON: But just be aware, again, just for whatever it's worth, especially for our writer, but that, again, the data that I've seen recently is that half of the American people have functional difficulty with health literacy. That means reading the front page of the newspaper and it means interpreting correctly a bus schedule. Can you imagine what this material will mean in that context?

DR. LEWIS: I have a whole bunch of literature on patient teaching for patients with low literacy levels that I'll give you some references to.

DR. FEIGAL: I just would say, though, there's a tremendous need for health professionals to see this information, and so to say that we can't make it available to them because patients might actually read it is difficult. I think it calls for the need to develop patient-related materials.

DR. McCABE: Yes, but I think the key thing is that if we have information, it ought to be available,

because we know other information will be available on the Internet and we need to have something that is perceived as objective, even if it's not at a literacy level at the first pass that would be readable by the majority. But it's better to have something there than nothing.

Pat, you're going to have to leave soon, so I'll give you a final word before you leave.

DR. CHARACHE: Thank you.

It really fits under Item 6, I think, of this particular initiative, and that speaks to the Laboratory-Consortium Working Forum that met yesterday. This is different, but overlapping. It's a Venn diagram with the concept of the forum that we've talked about for data collection and for various sensitivity issues. I found it very productive, in that it's laboratory-oriented in addressing many of these issues in a manner that I think would continue to be helpful to this committee.

If this group feels that it would be useful, then perhaps as the advice was made to have the other consortium go forward, it might be useful to suggest that such a consortium group continue to advise. It may be premature to do that, but I just wanted to raise that question.

DR. McCABE: My memory is that we did not recommend for the consortium to go forward as a separate consortium.

PARTICIPANT: You mean a data working group?

DR. CHARACHE: Well, no, I don't mean the data working group. I mean the group that was pulling together the FDA and the CDC and the other groups.

DR. LEWIS: The lab working group.

DR. CHARACHE: The lab working group.

DR. McCABE: Right, okay.

DR. CHARACHE: And the question was whether this was or was not useful to this body.

DR. McCABE: Yes, I think we recommended that, at least at this point in time, that we be the group that would try and coordinate, and at least at the level we can, that we would be able to identify some of the concerns that have not been recognized before.

Wylie?

DR. BURKE: I think we can refer to our discussion at our last meeting, where there had been presentations by some of the professional lab organizations, and then there was I believe a lunchtime meeting. In other words, I think we've already endorsed the concept that different bodies involved in lab quality assurance, that we would endorse their working together and coming up with joint coordinated solutions. So I feel like that's a done deal already and that that is a useful group for us to receive advice from or whatever the right way to say it is.

DR. McCABE: And in keeping with Reed's comments, it also brings some other people to the table as well that were a part of that group that aren't a part of this formally.

Yes, Pat?

MS. BARR: I think that the notion of that group, the thought that we've talked about a group that needs to look at data and how it will be used, is a way we could talk in the beginning of the report about public/private partnership and supplementing existing mechanisms in an inexpensive and efficient way.

DR. BURKE: With an emphasis on coordination as well as efficient use of resources already in place.

DR. McCABE: I want to point out one other area that we haven't discussed under 4, and that's Issue 4.5. We've talked about it, but I don't remember us coming to a conclusion, though perhaps others will.

That is, should genetic education/counseling provided by an individual with special training always be available when genetic tests are offered? Should this apply for every genetic test or only for some kinds of genetic tests?

Do we want to look at this in terms of what we want to say more specifically? Or have we said it and I've forgotten?

Ann, you want to comment?

MS. BOLDT: I guess in some ways it does get tied into the level of scrutiny that we're going to assign to some testing in terms of what we want to make recommendations toward. I mean, I do agree that there are some tests that can be done and counseled by a primary care physician that doesn't have a lot of training in genetics, but there's definitely some predictive testing that will need that level of high scrutiny.

DR. McCABE: The other thing is that I think we got some good feedback from the public on this. We have said all along that we need to get continuing feedback from the public, so I would like to suggest that this is also an area where we should continue to get input from the public, because they are in fact the people who are receiving this information and can best judge whether they were able to understand it or not. But I also want to build into our document the need for ongoing public input.

Victor?

DR. PENCHASZADEH: What I think we should call for is certainly for education and counseling. That should not be construed in the sense that every patient having a genetic test should see a clinical geneticist or a genetic counselor. I mean, we might talk about properly trained health professionals in genetics or something like that, but some explanation by someone, by a health provider, that is conversant on the genetic issues pertaining to that particular test should accompany any genetic testing.

DR. McCABE: Wylie?

DR. BURKE: Yes, I guess I would emphasize that point, too. That is, that what we need to emphasize is the importance of pre- and post-test counseling appropriate to the level of complexity of the test. It will be a continuum.

We've already said that we want to emphasize the importance of education in genetics for health care providers, growing technology, growing need to know, et cetera, and I think we have to be very careful about any kind of statement that declares who should do the counseling.

DR. McCABE: Plus I think we want to be careful also not to provide a roadblock, so that you can't put a test out because you don't have the person. And we don't have the personnel, really, at this point in time.

Somebody brought up yesterday, but I'll follow up, and that is is it appropriate, because of those concerns about personnel, to endorse a workforce study? Somebody raised that. I can't remember whether it was in the formal session or in conversation.

Yes, Wylie?

DR. BURKE: I actually think it's a point we should keep in front of us, but I think it's a little bit premature.

DR. McCABE: Okay.

DR. BURKE: Because a workforce study says that we already know what workforce we need, and I'm not sure we do. I think this is a sort of later subject for us -- health professional education, what would we consider adequate credentials for tests of different levels of complexity -- I think that's going to be a meaty conversation that we should have first.

DR. McCABE: Pat?

MS. BARR: I do think it would be appropriate in our report to say that one of the areas of access to tests is that counseling is not recognized as a reimbursable service, and that this is a problem and while it's not something we're going to deal with in oversight, it's a problem that we want to note because of public comment, which I think we did get.

DR. McCABE: Yes, I would say, rather than not reimbursable, because if we aren't specifying the profession, then I would say not adequately reimbursable, because in fact physicians can do this, but they aren't the most cost-effective providers of this. So if we could just make it adequately reimbursable, and then it's certainly true.

Ann, then Elliott, and then Joann.

MS. BOLDT: One thing we should utilize is the NCHPEG I know has come up with some core competencies for health professionals, and they actually have given a lot of thought to that. So I think we should reference that as at least a minimum standard for health professionals in terms of competence.

DR. McCABE: Is everybody comfortable with that without saying it? Or if we propose that we're going to discuss this in the future, we can allude to it now, and bring that document back to this group at a future meeting so that we can consider it before we just acknowledge it.

Elliott, you were next.

MR. HILLBACK: No, nothing.

DR. McCABE: Joann?

DR. BOUGHMAN: I was actually going to suggest that in the context of our recognition of the importance of patient understanding of this emerging field of technology and testing, and maybe be able to quote somehow that the challenges -- and there were a couple of interesting patient or consumer comments that I actually wrote down earlier and gave to Dr. Hanna about some of the risks and benefits would be understood better and would be balanced out if in fact this information were readily available or were available to the patients, and there was a nice way of putting that. I think in the context of this being so important, the NCHPEG, that they are working on it and we are looking forward to work products that come out of there, because of our recognition of the importance of this situation.

I think that hopefully we are going to put something not only down in the document, but up in front about -- didn't we say that this morning about educational issues and global issues? That came out in some -- maybe it was yesterday. It's all merging together -- conversations, but maybe we could refer back to that.

DR. McCABE: The other thing I'd just comment, really, for the author of this that Joann has gone through and I saw a nice annotation of the comments of various of the public in each of these categories, and so you ought to utilize that to help come up with those quotes.

Michele?

DR. LLOYD-PURYEAR: I disagree about not putting in stuff about for the workforce. I think, even given the genetic services legislation that's been proposed, training issues are not identified, and I think it's important to bring up as an important issue, that it needs to be looked at, but also in process of acknowledging some of the ongoing work.

And the other reason why to bring up workforce is that studies that have been done around workforce and genetic workforce in general have shown that there is no need, in terms of the formal studies that are published, and so I think those need to be counted and looked at again.

DR. McCABE: But I think one of the concerns is -- the way I understood it was that we were acknowledging that there are workforce issues, but we were saying that they are too complex for us to resolve at this point in time.

DR. LLOYD-PURYEAR: No, I didn't think we should take them on, but I thought that it should be acknowledged.

DR. McCABE: Yes, I thought we had agreed to do that.

Judy, and then Francis.

DR. LEWIS: I was going to suggest we acknowledge them and then say that that's part of our future agenda, that we know it's part of our priority list that we identified at our first meeting that we will be dealing with this as soon as we get this report off our plate.

DR. McCABE: Francis?

DR. COLLINS: I was waving, not asking to be recognized.

DR. McCABE: Now, we need some volunteers for Number 4. Elliott, Ann, Barbara, Victor, Kate. That was the Army-type volunteer I think there. We assign you to volunteer for this. Anybody else?

(No response.)

DR. McCABE: Okay. Again, everybody will read everything, but I want some people who will really focus on some specific areas.

Let's move on to Number 5. Issue Number 5. Appropriate level of oversight. We have yet to discuss the threshold. We have said that, you know, we'll have different levels of threshold. I don't know if we're going to be able to discuss the specifics or if those are going to have to come up with practice, but I don't want us to leave them out by ignoring the issue. If we decide to not get more specific, I want it to have been a discussion that we're not going to get more specific.

But Number 5. Appropriate level of oversight, and we basically said different levels of oversight for their different purposes, different stages of development, and that we needed to look at the public comment before we were ready to formulate or offer any views on whether additional oversight is needed. I certainly think that we've agreed. All of our discussion has been that there's additional oversight.

We've discussed some recommendations to the agencies that already have regulatory authority, that they need to be sure that they have adequate resources to carry out their oversight in the genetic testing area.

The public, there was some tension in terms of increasing oversight and losing tests, and we got that from a very well-organized community, the hemochromatosis community, but it was in other commentary as well.

So some discussion on this. Judy.

DR. LEWIS: I think those are two issues. I think that oversight can be accomplished without removing of tests, and I think that what we have to do is just talk about the fact that there will be different thresholds that will require different levels of oversight, and that some of the things that we've talked about may require additional oversight without actually coming out with like a schedule of drugs.

So I would like to see us address the issues without getting incredibly specific about what tests fall into what level, and I think we've done a pretty good job of discussing what are some of the things that might require increased oversight, both in our consultation document and in our discussions.

DR. McCABE: Francis?

DR. COLLINS: I think this really is sort of the meat of our recommendations and I hope we don't skirt too far away from actually saying what we think, and I guess my take on the conversations we had over the last two or three hours were that -- so I'll make this proposal, and then you all can see whether you think you agree with it -- that a newly developed test that is predictive and which is for a condition where

an intervention has not yet been validated ought to be subject to an oversight that is greater than what currently exists and, to be more explicit, ought to be fed into the FDA review system.

DR. McCABE: The axis that you didn't discuss there, but I think we had some discussion earlier today, and that was the penetrance issue, and I'm not sure that should a part of that, but I just wanted to acknowledge.

DR. COLLINS: Yes, I left it out because, again, I'm not sure whether high penetrance or low penetrance is the one that worries me more in that circumstance. So that's why I left it out.

DR. McCABE: So predictive tests without an established intervention should have a high degree of oversight, a high priority for and a high level of oversight. Is that --

DR. COLLINS: I was even more explicit and said they should go through FDA review for a newly developed test.

DR. McCABE: Wylie, and then Barbara.

DR. BURKE: And I think we can add that we developed a list of criteria for review, and I think those criteria, the way we would add to the sense that Francis just gave us is in addition tests that don't, by their nature, call for a higher level of review would do so if they raised concerns under the following categories.

DR. McCABE: Barbara?

DR. KOENIG: I'm going to pass.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: It depends on how you define intervention, and it's only because the Fragile X Foundation and Congress' mandate that we look at fragile X syndrome to do newborn screening, and when I talked to the parents and raised that, that there was no intervention, they said, "But there is," and the intervention is that, because there's a psychological overlay within that syndrome, that having psychotropic interventions was -- I mean, that was their explanation.

It's not as simple as proven intervention or no intervention, because that sometimes, that's like high risk and low risk. I mean, it's subjective.

DR. COLLINS: We can talk about that being a spectrum, and not all or none.

DR. McCABE: Yes, Wylie, and then Victor.

DR. BURKE: I think that's where quality of evidence is really crucial. I think if that's hearsay, if that's opinions of parents or docs, it would be hard to sell, whereas if there's outcome data that documents that there is a difference in outcome when a kid is diagnosed by a genetic test early and provided with certain kinds of interventions, that becomes very powerful evidence in favor of an intervention.

So to some extent, when we say whether or not an intervention is available, I think we have to link it to what kind of evidence do we require to make a statement that intervention is available. I don't think it's going to be a randomized controlled trial, but it's got to be something better than anecdotal evidence.

DR. McCABE: Victor?

DR. PENCHASZADEH: Well, I think that the key criteria here for a high scrutiny test, it's more than whether there is a known intervention. It's whether or not you are actually predicting in a healthy individual, because actually there may be an intervention, but why would you subject a patient to an intervention just by predicting something if that person doesn't need it?

But if there is no intervention one can think of that is totally innocuous -- all interventions have their benefits and risks, so I would take the question of whether there is intervention or not out of the requirement for higher scrutiny simply if you are doing the predictive testing on asymptomatic individuals.

DR. McCABE: Do you want to respond to that, Francis?

DR. COLLINS: Again, I think that comes down to what's the quality of the evidence that the intervention has value, and part of that maybe intrinsically includes what's the risk of the intervention as well. I mean, I take your point.

But I guess I'd worry about a system that treated equivalently a circumstance where you did have a very clear, known intervention -- and hemochromatosis I guess could come to mind here -- as opposed to something where you have absolutely nothing, like an APOe4 test. It does seem to me that those are intrinsically and intuitively in somewhat of a different category as far as the amount of oversight you'd like to see applied, and I hate to lose that altogether, although I take your point.

DR. McCABE: Elliott, then Barbara, and then Wylie.

MR. HILLBACK: If it's just predictive and low penetrance, then your assumption is that it's not very useful, and whether there's a treatment or not is probably irrelevant in that case. But I don't know how low penetrance and predictive plays with safe and efficacious, because that's the phrase that FDA, if they are the parties, will relate to, and I have no idea how to fit those two things together.

DR. McCABE: So just to try and capture this, then, what you're really talking about is a predictive test of penetrance that -- in other words, there's an intervention, but you don't know whether you should use the intervention, based on the penetrance for that predictive test. Is that fair?

DR. PENCHASZADEH: What I'm saying is if you have a predictive test on the basis of which you are going to do an intervention, that predictive test should have a higher scrutiny than a diagnostic test.

So what I'm saying is that the predictive testing should always have higher scrutiny, whether or not there is an intervention, because interventions will be done essentially probably on asymptomatic individuals, and you want a higher degree of certainty, of scrutiny, or of everything before you subject people who test positive to an intervention and leave people who test negative out of an intervention.

DR. McCABE: Elliott, did you have anything else to follow up on that?

MR. HILLBACK: No, I was interested in David's -- you know, how do you relate a situation that is, as Francis says, predictive and low penetrance with safe and efficacious, and where do you get to the point that it could get approved in that environment? Why don't we just wait until we have a lot more data, many, many years of data?

DR. FEIGAL: The evaluation of a diagnostic test isn't just safety and effectiveness, as you know, because we start with the analytic validity and the sensitivity and specificity, but then I think you sort of look at consequences of misinformation, if you will. That's the safety issue.

A concrete example of sort of how the thinking with this goes, if you look at the current diagnostics for Lyme disease, the sensitivity and specificity is such that they're not very suitable for use in the general population, but they're great as a confirmatory test when you've got other evidence and the prior probability is higher than it would be in a general population.

That's sort of the context where we think about, well, what would be the consequences, and safety in that setting, if it was to be used as a screen, would be the consequences of people being misdiagnosed, of having extra tests, of all the consequences of being worried well with a disease.

So that's the way that we approach the safety issue, and efficacy is good information.

DR. McCABE: Barbara, then Wylie.

DR. KOENIG: I just want to support what Victor has said, and on a slightly different basis, in terms of the issue of an intervention being available is also crucial, I think we have underestimated the consequences of simply conveying to someone this kind of risk information, and essentially the whole notion of, as you said, the worried well or the living one's life at risk sort of phenomenon. We don't know that much about it, it's very complicated, and I think it's very important and it's very important in and of itself.

DR. McCABE: Well, would it be fair to say -- I haven't forgotten you, Wylie, but would it be fair to say that certainly if you have a predictive test where there's no proven intervention, you're extremely concerned, that another level of concern -- that then predictive testing in general we are also concerned about, but certainly those without intervention, those should -- and that was really I think Francis' point.

DR. COLLINS: Yes, I think if we just amended our criteria in there about intervention to include the words "safe and effective intervention," and then recognize that we are talking not about a binary category of yes/no, but a gradation of yeses, as well as some resounding noes, then I think we've captured that. Just an intervention -- I take your point, Victor -- understates the complexity and the nuances of what goes into whether that is a satisfying, resounding situation or whether it's actually more risky.

DR. McCABE: Are you comfortable with that, Victor?

Wylie, then Joann.

DR. BURKE: I'll just note that the word "safe," we have to be a little careful. There are certainly some

interventions we use that aren't safe -- that is, they have clear risks -- and yet we use them because they also have powerful efficacy.

I think it's reasonable to say that a predictive test should receive more scrutiny than a diagnostic test, as we've defined them, and that predictive and low penetrant are of concern, but I think we can look to the analogy of hypertension to show that it really is a matter of evidence. Hypertension is a predictive condition of low penetrance and we know that it's good to find people that are hypertensive because we have very good quality randomized controlled trial data that says if you treat those people you get better outcomes, even though only a minority of people with hypertension will ever have the bad outcomes we're trying to prevent.

There will certainly be genetic tests that fall into that category. So to me, I think the issue of interventions is important and it has to be tied to evidence quality. What interventions do we have and what do we know about them that enables us -- and we need higher quality of evidence the more we're dealing with predictive conditions of low penetrance.

DR. McCABE: Joann, did you want to say something? Okay, Victor.

DR. PENCHASZADEH: A follow-up. I would like to ask Francis if he would be as specific to recommend the FDA approval also then on the predictive testing, even if there is safe and efficacious intervention.

DR. McCABE: Well, my understanding is that there will be FDA approval under the regulatory authority. It's really in terms of prioritization is what we're talking about.

Is that fair, Francis?

DR. COLLINS: I guess I didn't realize that we had decided that all new tests would go through FDA approval. I thought we were trying to decide something about the prioritization or maybe the threshold, and I thought we'd start the discussion, and we sort of did, with the case of most concern and then we'd think about how much less concern sort of situations would you get to before you decided this doesn't need that kind of very elaborate, potentially heavy-handed review. I mean, this is the crux of our whole question here about high versus low scrutiny, and we're at it, but I didn't think we'd decided to throw the scrutiny issues out in terms of whether FDA gets involved or not. I thought that was still on the table.

DR. McCABE: Joann?

DR. BOUGHMAN: I just wanted to bring us back for just a moment to the issue on page 15 where we said we needed public comment, but remind us that the Surgeon General, on the morning of the 27th, made in his introductory remarks a couple of pretty strong statements about the role of protection of the public, but in fact in putting those comments together with the comments, especially from the hemochromatosis population, that as these tests and processes are being looked at and as the tests are being evaluated, the downside of the consequences of doing the tests also have to be weighed with the upside of having the test available to people, rather than having no test available, because that would be the option and I think we are in a situation where we have benefits and risks on both sides.

DR. McCABE: Elliott, Ann, and then Judy.

MR. HILLBACK: I pass.

DR. McCABE: Ann?

MS. BOLDT: I guess one thing in terms of the predictive testing in terms of having effective treatment or surveillances, I get reminded of early childhood testing, and I think that's important enough to make some type of comment about that, and the importance of also considering that with our tests.

DR. McCABE: So the statement being something to the effect that it's appropriate to test children when there is an intervention.

MS. BOLDT: Right. Like FIP. I'm thinking about that. Possibly doing that before 18 versus later.

DR. McCABE: Judy?

DR. LEWIS: I think we need to remember, too, that the public told us that for many people, even if there aren't interventions, that we shouldn't just deny them access to information, because for some people information alone is what they want, and I think that came across pretty clearly from some of the public, that information was an end in and of itself, and that for us to decide when it was appropriate to be tested, whether or not there was an intervention, that that was their concern. But I heard -- what?

MS. BARR: The only problem with that is that the people who were saying that were not dealing with predictive diseases. Well, or they were not dealing with complex low penetrance situations.

So I think we need to really distinguish that, because there's a point at which gathering useless information is not a good idea, and that's when you want to protect the public, and so some of these tests, in terms of having it and then not having a clue about what it means, because we aren't there yet, you just don't make it available for its own sake.

DR. McCABE: Francis, there's been enough discussion of your point. Do you want to restate it? And perhaps we should do it as a motion.

DR. COLLINS: So you mean going back to the proposal that FDA take primary responsibility for reviewing a new test that has this set of characteristics that would make us most concerned? That's the point you're talking about?

DR. McCABE: Yes.

DR. COLLINS: Okay. So as a motion that the FDA be assigned the primary responsibility for the review of a newly developed genetic test which is to be used for predictive purposes and for which a safe and effective intervention has not been proven.

DR. McCABE: Do I have a second to Francis' motion?

DR. BURKE: I second.

DR. McCABE: Wylie seconds the motion.

Discussion? We've been discussing it, but let's discuss it now as a motion.

Yes, Elliott?

MR. HILLBACK: Whose responsibility is to define safe and effective? Is that the lab's to come forward and show that there's a safe and effective?

DR. McCABE: David, how is that done now?

DR. FEIGAL: It's always done in the context of the treatment of the -- we're talking about safe and effective treatments, right? And the treatments are available at the time of the evaluation of the question. So what's safe and effective for hypertension now is different than what it was 20 years ago.

MR. HILLBACK: But if we wanted to bring a test through, then I guess as part of our file we would have to help prove that there's a safe and effective --

DR. FEIGAL: No, I don't --

DR. COLLINS: Notice, this motion applied to those circumstances where there was not a safe and effective intervention available. We haven't gotten to what would happen if there was. We should get there soon.

DR. McCABE: So it's good that we understand the limitations of the motion as well, and we can then get to a subsequent one.

DR. PENCHASZADEH: (Inaudible.)

DR. McCABE: Well, I mean, the issue is do you want to discuss it in the context now or do we want to then come up with another motion following on?

MR. HILLBACK: What tests would be there now that are on the horizon? Would BRCA1 be in this category?

DR. COLLINS: I think most people would say we don't have evidence that a safe and effective intervention has been proven for BRCA1.

MR. HILLBACK: So we still would have to take that through FDA and we probably then would not have a test available today.

MS. BARR: No, it doesn't mean a test isn't available. It just means it gets looked at.

DR. COLLINS: You're doing the gloomy thing again.

MR. HILLBACK: I am, because I don't think we've thought about the implications of what we're doing.

DR. McCABE: Plus, what we're saying is that a new test --

DR. COLLINS: A new test.

DR. McCABE: A new test.

MS. BARR: Let me do BRCA1. There was clear evidence that there was a relationship and a predictive value of BRCA1 in very high-risk families. Immediately, as that was established, I think there was enough evidence to begin using that test clinically in those families. Research was going to also continue, but there was good reason for genetic clinics to start using that test in those families, and only those families.

Unfortunately, what happened is the test was marketed to larger numbers of groups. The definition of what high risk was was not properly articulated and it was articulated differently by many different labs, and then statements were made about all Ashkenazi Jews. Lo and behold, you did a little more research, not true.

So I think it wasn't that the test wasn't available. It should have been made available, but it should have been available appropriately, and then, as you wanted to make it available to more people, you needed a responsible data collection mechanism and a clarity of what you could tell them and couldn't tell them about its effectiveness.

DR. COLLINS: Well said.

DR. McCABE: You're calling the question?

MS. BEARDSLEY: No, no. I'm asking to be on your list. That's all.

DR. McCABE: Kate?

MS. BEARDSLEY: I just wanted to make sure that I understand what we're doing here. On Joann's chart, we essentially had I guess four points. We had a research point, we had a limited use point, we had an approval point, and we had a post-approval point.

I have been assuming that we're saying that there would be some review and that it would be an FDA review before there could be limited use. Is that right? Is that what we're saying? Okay.

DR. LEWIS: For those tests.

MS. BEARDSLEY: Not approval.

DR. McCABE: For the tests as described by Francis.

MS. BARR: But what about when we said there was going to be independent review of all tests?

MR. HILLBACK: We haven't decided which mechanism. That's what Francis said a minute ago.

DR. COLLINS: Right. So I thought we would start with sort of the extreme end of the categories here and see if we could agree on that, and then we'll step back, recognizing that we did already say that there

must be independent review of all tests.

DR. McCABE: Let's vote on this motion then. The motion does not exclude additional motions, but the motion is stating and is taking an extreme example.

All in favor of the motion, please raise your hands high.

(Show of hands.)

DR. McCABE: Opposed?

(Show of hands.)

DR. McCABE: Two opposed.

Any abstentions?

(Show of hands.)

DR. McCABE: One abstention, Barbara.

So the motion carries.

Now, are there some additional motions?

MS. BEARDSLEY: Can I explain my vote?

DR. McCABE: Sure. Yes, you can explain a vote. Please explain it briefly.

MS. BEARDSLEY: I will.

I'd like to explain my vote. I'd like to say that I think if someone is going to review tests, particularly high scrutiny tests, it should definitely be FDA because they're people who know about this, but I think it's going to be very difficult to get tests on the market if they have to be proven to be safe and efficacious in the terms that FDA generally applies that standard.

DR. McCABE: Barbara?

DR. KOENIG: Just to explain my abstention, it's because I am really more in favor of Victor's point. I think any predictive test deserves a higher level of scrutiny, regardless of how one thinks about interventions that are available.

DR. McCABE: Well, let's proceed with another motion now.

Yes, Wylie?

DR. BURKE: I'm really going to make a motion just to clarify a point. We've already voted that we

think all new tests -- I'm going to limit this at this point to new tests -- coming to market should receive independent review. We've already begun to develop the sort of advisory guidelines that indicate what kind of factors go into that review and I believe this body should continue to do that.

With that in mind, I am going to move that FDA be the point of independent review for all new tests.

DR. LEWIS: Second.

DR. McCABE: We have a motion. It's been seconded. Discussion?

DR. COLLINS: That would not exclude, your motion, Wylie, that FDA could, if they chose, deem some of that review process to other organizations.

DR. BURKE: Correct.

DR. McCABE: Further discussion?

MR. HILLBACK: Whether it's deemed or not isn't going to make it any easier to get a test done through a regulatory authority. If you look in the list that GeneTest provided of all those tests that are there now, forget that we've grandfathered those, the next 300 tests, most of them are not of the size that's going to go through that kind of scrutiny in an effective way. It's just not going to happen, I'm sorry.

DR. McCABE: Michele, then Francis, and then Pat.

DR. LLOYD-PURYEAR: But Elliott, no one's laid out -- at least I don't think they have -- the criteria for what becomes FDA approval, which answers you, Kate.

MR. HILLBACK: Well, this is their device --

DR. LLOYD-PURYEAR: Well, but I think that that can be --

MS. BEARDSLEY: I wish we would lay that out, because that would make me comfortable.

DR. LLOYD-PURYEAR: Because we're saying what tests should be reviewed and we've laid out criteria for review, but we're not saying on what level.

MR. HILLBACK: Why would it be done?

DR. LLOYD-PURYEAR: Well, because I don't know that.

DR. McCABE: Francis?

DR. COLLINS: Well, actually, I was going to ask FDA to hear what your response would be. I mean, can you imagine setting up a deeming process that is fairly streamlined for tests that are of a lower concern for the kinds of criteria we've talked about all day today?

DR. FEIGAL: Well, the framework for farming out work, if you will, is that they're going to do the same

work you would. So the question really is whether we would have a streamlined process as well, and then whether or not someone else could do it for us is something that we're comfortable with. So your real question is do we have ways of treating different tests in different ways and streamlining things.

There are a variety of different regulatory methods, depending on the test. There are special procedures that are available for conditions that are used rarely, the humanitarian device exemption, which actually does not require any evidence of efficacy, but requires ongoing informed consent and IRB oversight. There is a difference in the 510(k) process and the PMA process of application.

I think in general our approach to products is to take a risk-based approach, and some of the criteria you've been talking about are the same kind of framework that we approach products with, and our general approach is to start with the highest risk, most problematic products first. When there already are products on the market, we often will establish a grace period, during which time the products can continue to be marketed while evidence is put together.

I think there are opportunities to look at ways of developing certain standards and trying to find out ways -- one of the approaches in regulation worldwide is to develop standards and ask people to certify that they conform to those standards and be willing to be inspected against that conformity. I think you could argue that in many ways CLIA is just such a program. It has certain standards and people mostly do their own documentation that they certify. So some of those standards could be developed over time.

I think I would agree with the doom and gloom if we said we can immediately institute this and not have to face such a program and not have to think about what it is that we need to streamline.

I think at the same time I guess my question to Elliott would be what is it about these tests that makes them have a lower standard of evidence than all the other tests that get introduced into the market? And whether or not in fact the use of home brew has been kind of a perverse incentive that's allowed well-funded companies to essentially hide their products from oversight and not pursue in a responsible fashion the same kind of regulatory standards that other companies are willing to pursue. It argues for a different level of concern for the public health.

MR. HILLBACK: I don't accept that at all, obviously.

If we were to go through the process as you perform it today at FDA, none of these tests would go through, because there's no one that will spend the money in order to not make money. There's not a single test, including cystic fibrosis, that has got enough volume to go through the cost of doing the study as required.

We have all complied in every case with the CLIA regulations, which are the law of the land, and we have been very careful to go through and are able, if CLIA inspectors come, to show them that we have a test that meets all the requirements, which are that we can prove here's what we can test for, here's what we can't test for, et cetera.

So I don't accept that we've used it to hide behind. There isn't another alternative.

You know, we do a lot of tests. We do 50 a year or 20 a year. There's no economic way to do a clinical trial of longstanding, to follow patients, and submit that. It's not going to work.

What we count on is that other people are doing the clinical work in most of these cases, and that we're citing other people's work to say there's a correlation between this mutation and a disease, and then using that basis we can develop a test, like many other labs do.

We're better off than -- you know, we're right there with Mayo and Baylor and a couple of other labs. Look at the other hospital labs that are doing these tests. They have no resources to do this. So it's not mostly major corporations. I think there are only three major corporations with DNA labs today.

DR. FEIGAL: Well, I think that the issue that you raise is really one of those tough choices. I mean, you've made the case that you don't even have the resources to find out if clinically these things work, but you feel that these things should be on the market, but how we tell the patients is -- I mean, your best advice would be, well, you can look at the same stuff we looked at and take your chances.

MR. HILLBACK: No, that's not correct. We provide genetic counseling with every test that we put out. We either talk to the doctor and have them make sure they're going to do it or we do it ourselves.

DR. FEIGAL: Then I misunderstood you. I thought you said you didn't evaluate the evidence.

MR. HILLBACK: We evaluate the evidence that other people have done the research on. We don't do the research ourselves, and so we're dependent on the rest of the medical community to develop evidence, and then that's how we pull it together.

So we have data and we can provide that, but I asked you earlier if we had cites of a couple of papers that had been done, and you said that's not normally what you take. You'd want to see something more than that.

DR. FEIGAL: Well, we usually look at the original data. I think if you look at the so-called peer-reviewed vanity press literature that is largely financed by the companies whose products are written about in that literature, I think you'd find some interesting discrepancies if you'd take the trouble to get the data.

DR. McCABE: We need to broaden the discussion here, so I have Pat, Victor, Ann, and Wylie.

MS. BARR: I guess I'm looking for some understandable compromise between what has been articulated as two positions at a distance, and one of those might be, it would seem to me, since you're already saying FDA is not going to be able to review all of these things, you're going to review the ones of greatest importance first and work your way down.

The other is is there a mechanism -- I know you have panels for review when devices come through or whatever. Is there a way to set up an early genetics test review panel that addresses criteria similar to the criteria that we have articulated here and can go through those things with some rapidity, and say that because we, as an advisory group, are saying that this is the equivalent of safe and effective in this new technological area that that will satisfy FDA and they can also deem associations to use those same standards.

I mean, I think this has happened in OPRR, too. You take a new technology with new understandings of how it's going to come into the market and use it, and you lay it on top of an old framework, and it's not

always the best way to do it. You are the best agency, it seems to most of us around the table, but we would like you to be able to use the parameters of what you're supposed to do within the context of new technologies.

DR. FEIGAL: Well, my question, I guess, to the panel, given that we approve about 1,000 tests a year, and for the ones that are done in the 510(k) framework, an average review time is about 55 hours. So if you want to volunteer to do this, that's what you're volunteering to look at. The PMA is quite a bit longer than that on average, although not so bad for in vitro diagnostics.

In contrast, the CLIA review is about an eight-hour inspection. Is that right?

MS. YOST: It depends on the site.

DR. FEIGAL: It depends on the site. Every two years for maybe 1,000 tests in a given laboratory. It's a different level. They're looking at process. They're looking at different kinds of things.

But my question, I guess, to the panel is are there any genetic tests that you feel are important enough that they would meet our usual standards? And if not, then you should look for lower standards and advise us to find mechanisms to apply the lower standards to those tests.

Now, it may well be that the unique situation of the rarity of the conditions creates the rock and the hard place where you have to say the usual paradigm just isn't going to work. There may be other settings where it's a high volume setting and there really isn't any excuse not to collect the data, and it will be billed profitably and it will fit the same old paradigm.

The standards are not just safety and effectiveness standards. They're also manufacturing standards. These are consumer protections that we didn't invent. These were put in place by Congress because it was felt that this was what the level playing field demanded, that there be a certain level of quality for tests that were going to be marketed in this way.

DR. McCABE: Victor? I've got Victor, Ann, Wylie, and Kate, and then we're going to need to vote and move on, so please be very brief.

DR. PENCHASZADEH: Yes, very brief.

No, I just wanted to state my opinion that I don't see any other agency that can fulfill the task and the role that the FDA fulfills now. So it's kind of as simple as that.

Now, I'm kind of persuaded by what I'm hearing now and what I've read before about possible exemptions, humanitarian device exemptions, the deemed process, and perhaps we could also in trying to bridge the gap here one could try to make recommendations for -- because some of the hurdles seem to be due to resources available and perhaps we should make recommendations that resources be made available to the agency so they can perform the task, or entice them to streamline their process, particularly for tests that are deemed important and should not wait too long.

That's all.

DR. McCABE: Ann?

MS. BOLDT: I guess my question is is there an application cost to go through an -- so that's not going to be a deterrent for small labs. Okay. I was wondering if that would be something that they wouldn't --

DR. FEIGAL: It's the data.

MS. BOLDT: Right, the data. I mean, is that something that we want to put something in in terms of waiving -- can we waive that fee? Can we have support of the government?

DR. McCABE: It's not just that. It's the time.

MS. BARR: David says 55 hours for them to review it, but ask a drug company how many hours and how many dollars to get it ready so they can review it. They'll tell you in the order of $5 to 10 million is what they throw out per test, but that's because they're doing a number of tests and they weed it out.

DR. McCABE: Wylie?

DR. BURKE: Certainly, implicit in my thinking in proposing this was that there would be a process developed that's appropriate to genetic tests and appropriate to the level of complexity of the test.

I think what I'm looking for is basically a prospective review by individual test of the very kind of data that CLIA asks labs to produce. I don't see that we need for most genetic tests to produce information other than the kind of information that CLIA asks labs to produce. I think we've already heard that published data on the clinical relevance of the test, is relevant. We can't say that any peer-reviewed article will do, because there are plenty of peer-reviewed articles that don't make a strong case for genetic tests.

But the point is I don't think we're saying that a lab, in order to go through FDA, ought to have to do their own clinical study, nor really provide more data than they would normally have to put together for CLIA, but what we'd like to see is a prospective review that looks at that data and passes on it before the test goes out to the public.

DR. McCABE: Kate?

MS. BEARDSLEY: I guess I'd like to ask a couple of questions. One thing we haven't talked very much, but David touched on, is manufacturing standards. FDA generally has very stringent manufacturing standards, and I would think, although I don't know for sure, I know it's true in other contexts that academic labs, for example, generally don't meet FDA's manufacturing standards.

I worry very much that in applying the full range of FDA requirements here that we're going to, and we've seen it in other industries, we're going to push out the small guys and the academic labs and we're going to end up with all of this in the hands of big companies.

I appreciate what you're saying, David. You know, the test is for people and the test should be as good -- you know, it should be the same for everybody, and on the other hand, I really hate to see the incentives for academic and small labs go away, because I think that's a source of a lot of innovation in genetic

testing.

DR. McCABE: Elliott, and then Judy.

MR. HILLBACK: Yes, I think I'd like to make a couple of points. One is I think in some ways we're throwing out the baby with the bathwater here. I think if you go back patients have been generally extremely well served by the genetic testing laboratories we have in this country that are governed by CLIA regulations, which you seem to discount totally in their ability to manage any of this.

And we're now talking about changing an entire process for what may be a few percent or some subset of the test where people have significant issues. I'm not sure I agree with those, but I would argue very strongly that if we don't separate these groups and deal with most tests in one fashion -- and Wylie's point of if we could do the kinds of things we do for CLIA and someone looks at it ahead of time in that regard, but I believe we'll end up at Section 809.10 doing everything that the device manufacturers have to do for a kit, and if we're in that circumstance, it is more than 55 hours to put that file together for them to spend 55 hours.

I thought this was where Francis was going originally. I still disagree that FDA is the right group anywhere here because I don't think they're as flexible. We get into the issue like we have on the CF test where we've made 10 additions to the test in eight or nine years. Would we have delayed each of those by a few years? I don't know. Maybe not. Maybe there's a way we can work with the agency to do that.

But I really think -- you know, I'll give up on a few tests, but if we put them all through there, I think we're creating a very difficult situation just to try to solve a few problems.

I read all the comments -- I'm sorry. One more minute. I read all these comments and when you look at the comments from the public, the biggest comments are not at all about quality of tests or risks there. They were about stigmatization, they were about confidentiality and privacy, and now we're going to turn the system upside down and I think do a disservice to the patients, not a service to the patients, in general.

DR. McCABE: Judy, then Francis.

DR. LEWIS: I think the issue is evidence-based practice, and I think the issue is, what we have to do is we have to have enough evidence to say that what we're doing is what we say it's doing. We're saying that there needs to be an independent review for that.

I think the assumption that the process is going to have some burden on the proposer is reasonable. I think the issue is that FDA can develop a process that's going to work, and we're going to work to make sure that the process isn't something that is overly delaying, and what I'd like to see is the same data set be available for approval and ongoing oversight, so that maybe FDA and CLIA can get together and come up with what the data elements are, so that you do it for initial approval and then for continuing oversight we've got the same elements.

But to me, the issue is that there's got to be some kind of evidence-based practice and we've got to have some kind of independent review, and the FDA model seems to be the one that people are saying works the most, and I would hope that it would be one that would be appropriately protective of the public, but not one that is so incredibly --

PARTICIPANT: Complex.

DR. LEWIS: Complex is a good word, or onerous is a better word. That it restricts progress unnecessarily, and I think that's a fine line and I think that that's going to be part of our ongoing oversight, and maybe what this committee needs to do is continue to monitor the process with the sense that if it gets to the point where it is delaying appropriate progress unnecessarily, that then we revisit it, but that we have to put something in place for evidence-based practice.

DR. McCABE: Francis?

DR. COLLINS: I agree with that, and actually I thought Pat Barr enunciated a sort of friendly amendment to Wylie's motion, and I might ask, if you're willing, Pat, to reenunciate that, perhaps even in the form of an amendment to Wylie's motion if you're comfortable doing so.

It's a clear sense that I hear all the way around the table that the goal here is not to gum up the works with a whole bunch of bureaucratic barriers that we didn't intend to produce simply by using the very rigorous tool called the FDA to try to make sure that we're paying attention.

So is there a way that you could in fact put that forward?

DR. McCABE: Pat?

MS. BARR: I would be delighted to if they could find it on the tape.

DR. McCABE: You were shaking your head. Do you remember?

DR. BURKE: I think it simply had to do with stating the assumption that the FDA would be flexible to develop a process that was appropriate and that in particular was appropriate to different levels of complexity of the genetic test.

MS. BARR: But I'm not sure we got an answer from the person sitting at the table who had to answer.

DR. BURKE: Right. The question is is that a reasonable expectation?

DR. FEIGAL: Could you rephrase it again?

MS. BARR: What I said is that we know we want independent review. We believe that the FDA is the agency that will conduct that independent review. We as a working group are working very hard to establish the criteria that we believe are reasonable and can work with FDA to establish standards to measure that criteria, and that we would view not as onerous, but would be evidence-based, and that in that context could FDA be the administrative agency through doing it themselves and through deemed professional groups to move tests from research stage to clinical stage for particular purposes with appropriate labeling?

DR. FEIGAL: There are a lot of parts to your question, so thanks for restating it.

One part of it is can we use standards, so that people can state that they are conforming to a standard

instead of submitting all the documentation? Yes. There would be a need to develop those, and, of the over 500 standards that we have accepted in different product areas, we have had a role in writing very few of those. We have taken them from outside bodies and that helps streamline the process. The kinds of evidence and so forth that could be considered, that all can be part of that.

Part of what you have to consider, though, is when you have standards, at what level does the evidence base leave the judgement of the laboratory and become the judgement of the overseer, whether it's CLIA or whether it's us?

So that's at the level where I hear from Elliott that it's very burdensome to put that kind of evidence together in an application and to lay out exactly what is the evidence that supports it, as opposed to an approach that would say that if you assert that such evidence exists and you'll produce it on demand, which is a different kind of approach, you know, would that be an adequate standard?

That has not traditionally been the standard for either a PMA approval or for a 510(k) clearance, to have someone assert that it's there and trust us, and again I think if you go back and look at -- the "CLIA approach" is really not an approach that evaluates the evidence in detail test by test. New York State sounds like they do some of that, but that's not the purpose of CLIA.

In fact, if you look at Abbott Laboratories, which recalled 250 products, I don't think any of those had actions against them that were pending because of CLIA, even at a time when we publicly had six years of warning letters, public warning letters, about the quality of those products and even though that company, in withdrawing them, agreed to pay a $200 million fine for their violations of the law.

So the different regulatory groups do different kinds of things. Now, there we're talking about manufacturing quality, but I think it would interest you to read the kinds of defects that existed in those products that were not apparent to the states that licensed those laboratories or the hospital directors who used those kinds of tests. There are different standards, but you do have to apply the right level of standard to the problem that you're dealing with.

I think the question of how much of this could be done with a streamlined kind of fashion, we'd have to think how much of this could we collapse into standards that wouldn't be reviewed? That would not be reviewed. That's the only way to streamline it is to say we agree that all you have to do is swear that I meet this standard and we won't review it, because as soon as we have to start reviewing stuff, then we're preparing the application and doing the back and forth that I think Elliott rightly is concerned will interfere with the development of small tests.

DR. McCABE: I'm going to ask the next speakers to really limit their comments to about 30 seconds so that we can move on.

So Wylie, and then Reed.

DR. BURKE: I accept that. I think we are asking for that kind of streamlined process.

At the same time, I think I would acknowledge upfront there probably are going to be some pieces of evidence we will want a test developer to show us, whether by reference to literature, published literature, or whether by reference to their own work. I think our task is to make sure that that's minimized in the

streamlined process and that we focus only on those things where we think it's critical that evidence be displayed.

So I think you could have a standard-based approach and still have one or two items of evidence that you say, yes, got to show us that. Don't want you to do the test if you don't.

DR. McCABE: Reed, 30 seconds, please.

DR. TUCKSON: Damn. You have me rushing so hard.

I like what you said. I'm right there with you. I go back to a challenge Francis Collins gave us at the beginning of the meeting in Baltimore, where he said what process should determine if and how a genetic test is ready for clinical introduction? The marketplace, practice guidelines and professional standards, government oversight and regulation.

It sounds like you are willing, and I want to make sure, that you would agree to having some deemed status where you have professional standards from professional organizations a part of the process with government, so you get that input in, and if that's what you're saying, then I think I like what I've heard.

DR. McCABE: Briefly, Elliott.

DR. TUCKSON: That was under 30 seconds.

MR. HILLBACK: It was very good.

I think I would propose that rather than let's take a vote today on putting all of the tests under FDA -- I'm just going to tell you what I think. I get to say what I think. I do it once in awhile.

DR. McCABE: You have 10 seconds left.

MR. HILLBACK: I believe that the sense of the group is that we need some sort of premarket look, that some tests need the typical FDA look and some tests don't, and I think to then say, okay, well, we'll ask FDA to alter all their methods to do that, I'm not sure that's the best way.

I would suggest that what our proposal is is to say there is a category of tests that we think FDA should look at. There is another category of tests that we need to look at the combination of professional societies, CLIA, FDA, and see if we can find a mechanism that will work that is outside the normal FDA system, because we're already asking FDA to modify their normal system anyway.

DR. McCABE: So Wylie, you've heard a request for you to withdraw your motion or for it to be -- well, no. It was Wylie's motion, which you amended.

DR. BURKE: Respectfully declined.

DR. McCABE: Okay, but I think we also heard that there would be some work with the FDA to try and have this so that it did not create a roadblock and limit test availability. Everybody heard that also?

DR. TUCKSON: With professional societies also.

DR. McCABE: Yes.

Okay. So the question's been called. All in favor of this -- the motion has a friendly amendment, right, Wylie? Okay. All in favor of the motion as amended, please raise your hands.

(Show of hands.)

DR. McCABE: Hold yours up, Joann. I'm not sure that -- okay.

You got seven, Becky? Okay.

All opposed?

(Show of hands.)

DR. McCABE: One opposed.

MS. BEARDSLEY: And I abstain.

DR. McCABE: And abstentions. Abstentions?

(Show of hands.)

MS. LAWSON: Okay. Seven, one, one.

DR. McCABE: There was a question to my left about explaining votes, but that's really the individual's prerogative if you wish.

Do you wish to comment, Kate?

MS. CARR: Did you want to explain?

DR. McCABE: Do you want to explain? It's up to you.

MS. CARR: It's up to you, because you wanted to last time.

MS. BEARDSLEY: Yes, I'm beginning to feel happier about what I'm hearing from David. It seems to me that if you could deal with this largely in a standards way, that that would be good. I think the humanitarian device exemption is really useful for a lot of these tests, and I absolutely appreciate your good faith, but I'm not quite convinced that it's going to follow through to all of the people in your organization.

DR. McCABE: But the other thing I heard in the discussion was that the SACGT will be monitoring this.

Other discussions? Other motions? We have about 15, 20 minutes, and then I do want to move on to

future business.

Reed?

DR. TUCKSON: I ran through that 30 seconds business fast, but I just want to get a sense of do we really have a consensus on the notion of the idea of what the SACGT role will be vis a vis the consortium as it regards the answer to this Francis Collins challenge at the beginning of the Baltimore session? And I'll restate it.

DR. McCABE: First of all, let's clarify consortium, because I don't think consortium --

DR. TUCKSON: I won't use the word. That's what I'm saying. I'm not sure where we've come out, and again, what I don't understand is --

DR. McCABE: What are you referring to? What group?

DR. TUCKSON: Whatever is left -- whatever this non-governmental entity, which is us, okay?

DR. McCABE: So the Laboratory-Forum is one group or the SACGT.

DR. TUCKSON: Let me say then the SACGT. Is the SACGT, as we have had our discussions, saying that -- well, let me ask the question. What is the process that we have determined for determining whether a genetic test is ready for clinical introduction? The marketplace, practice guidelines and professional standards, or government oversight and regulation? Have we been clear it's all of them, it is a combination of them overseen by some -- how have we answered that question?

MR. HILLBACK: The FDA's doing it.

MS. BARR: Government oversight with the cooperation of -- through a standards mechanism where appropriate.

DR. TUCKSON: And the standards mechanism which includes what?

DR. BURKE: Includes the input of professional organizations.

DR. TUCKSON: I just wanted to get it in.

DR. McCABE: You know, I think that, as expressed, there is some concern about how the FDA might proceed, recognizing that we are advising the Secretary, who would then give you the marching orders. We certainly can't give you marching orders. It's not our role.

But it would be interesting to begin to talk, to perhaps have your group bring back to us the implementation of the discussion that we've just had, and I think it might make everyone feel -- well, we would at least feel that you were responsive, and it might reassure some of us as well. Perhaps not all, but some.

DR. FEIGAL: I'll bring someone besides myself who can present it. No, actually, we've been working

on some of this. Steve has been working on some of it, and we'd be happy to present that when there's some time to do that, and I think this group could help us figure out how to interdigitate some of these processes and how to work with our own Genetics Testing Advisory Panel.

DR. McCABE: Sarah and I have just conferred, and you will have the opportunity in May.

Wylie?

DR. BURKE: I also want to say for the record -- this is just in follow-up to Reed's -- that I want to make sure that we clearly document in the record that an important part of our conversation was not only that we would expect professional organizations to participate in the development of standards for the standards-based evaluation, but also that the SACGT would participate in that process, taking into our account our makeup, and therefore community input.

DR. McCABE: Thank you.

Further discussion or are we ready to move on? Are there things that we have left out? Are there important -- yes, Judy?

DR. LEWIS: We have those issues under Number 6 and I just want to make sure we address those all. I think we probably have hit on most of them, but I want to make sure.

DR. McCABE: The issues under Number 6. Is the public willing to share genetic test results? We have some feedback on that. We can certainly include that in the commentary.

IRB reviews I think we've discussed. Informed consent I think we've discussed.

Public obtain results direct from the laboratory. We haven't discussed that. Is that a future direction or did we want to deal with that this afternoon?

Yes, Barbara?

DR. KOENIG: I think that that's probably an issue that we need to at least have a preliminary conversation about that, plus the issue of home testing and the issue of whether there needs to be a health professional intermediary involved when these tests happen, and I think that the public commentary seemed to say that there should be a health professional involved. So perhaps we could just move forward with stating that as a principle at this point.

DR. McCABE: Does anyone disagree with that?

MS. BEARDSLEY: Yes, I do.

DR. McCABE: Kate.

MS. BEARDSLEY: I think there are probably a lot of tests in which a health professional needs to be involved, but I also think that there are some that aren't. I guess as a consumer I feel that there is information that should be available to me regardless of whether I hire a health professional, and I don't

know exactly where to draw that line. I don't know how to do that right now, but I believe that some of this information should be available without a health professional.

DR. McCABE: Pat?

MS. BARR: I was going to make the same point, that this is a continuum, again, and there are situations where our understanding of what a test means and its implications is high and there are situations where it's quite low, and in those situations where it's high, which is going to be changing over time, it seems to me appropriate that consumers have access to that information in meaningful and useful ways.

So I don't want to make a blanket statement. I want to make another statement that there is a continuum, it's circumstantial, and that we need to look at it in more depth.

DR. McCABE: Michele, and then Judy.

DR. LLOYD-PURYEAR: Never mind.

DR. McCABE: Judy?

DR. LEWIS: The example I'm thinking of are things like home pregnancy tests and some of the over-the-counter women's health products that have been developed where you can do the test in the privacy of your own home, but yet there's the dial-a-nurse on the other end of the line or the dial-a-health care professional, where if you have a question, you're not given a test with no resources, but you're not required to go through a gatekeeper.

DR. McCABE: Victor?

DR. PENCHASZADEH: Well, as a health professional myself, I don't see myself only as a gatekeeper for anything.

I really think that in most circumstances, I really cannot imagine any exception to this. Any patient or any individual who is interested in knowing something about his or her health or predisposition or whatever should be helped by being able to share or discuss or be counseled about those issues with a health professional. I have a hard time accepting otherwise.

DR. McCABE: So what I'm hearing is that it's going to be hard to resolve this in the next 10 minutes, but it's certainly something we should identify for future discussion.

Joann?

DR. BOUGHMAN: Maybe two minutes, but two points that address, first of all, start with Number 5. I think that our report should acknowledge our interest in the issue around patents, the fact that there were several comments made by the public around this issue, and that we have people going to the meeting next week and we'll be working on this issue. I think that needs to be in the report and may have to be modified in the review.

Under Number 1 --

DR. McCABE: Before we move on with that, then the people who are going to the meeting next week will be representatives of the SACGT, and we would ask that you then provide us with feedback at the May meeting. The people who are going to the patent are Victor and Francis, and maybe Ann Boldt.

DR. TUCKSON: I'll be represented there, and we're actually making a statement, but I'll be represented.

DR. McCABE: Thank you.

Sorry.

DR. BOUGHMAN: That's fine.

The other point, and I'm not sure whether we can make it here and other places, but one of the opportunities that we would have under Number 1 with the willingness to share genetic test results, brings us right back into the discrimination issue, and I think that that came through very loudly and clearly from the public comments that there are certain situations in which people do feel that they would or could, but until we have all of the protections in place, the public did have some concerns about the issues.

DR. McCABE: Kate, and then Barbara.

MS. BEARDSLEY: I was going to ask a question about whether we're prohibited from or whether we would be allowed to as a committee send a letter to the House and to the Senate.

MS. CARR: No.

DR. McCABE: No, we can't do that.

MS. BEARDSLEY: We cannot? Okay.

DR. COLLINS: But you can put in your report that this is an issue that needs to be resolved in order for the future of genetic testing to flourish in the way that this committee would hope that it would. I mean, you have an opportunity there to speak to the Secretary, and this report will get broadly disseminated.

MS. BEARDSLEY: But it's lobbying to actually send them a letter?

MS. CARR: Yes.

DR. McCABE: Yes.

MS. BARR: But we can make ourselves available for comment and public hearing, however, can we not?

DR. McCABE: Yes, yes.

MS. BARR: So we should do that.

DR. McCABE: But again, that would be not at our discretion. That would be presumably at the -- I don't know the protocol on that, but presumably at either their request or the Secretary's request. We can't

request that we go to them.

Barbara, and was there someone else who had their hand up? Barbara.

DR. KOENIG: Just a quick comment. I'm totally in favor of all the efforts to pass all kinds of anti-discrimination efforts. I just want to make the comment that it's not surprising that the public came back with a certain set of answers when the main sources of education in the area of genetics has really been a lobbying campaign by many sources to educate them about this particular element and risk in genetics and not others.

And so we don't take too seriously the fact that this was the main comment that came back from the public, since that's the main message that we've been feeding to reporters, those of us who do this work, for so long. I think that we need to take that seriously.

DR. McCABE: And I would suggest, that in keeping with this, that again we reiterate in our final document that there needs to be continued feedback from the public, and that we need to look at future opportunities, that the meeting in Baltimore, the Web site, all of that should not have been the only time that we get input from the public.

Joann, and then Judy.

DR. BOUGHMAN: Barbara, your point was very well made. The way that I worded that I think was in fact to utilize the fact that we heard some of these comments from the public as the starting point for our reasoning that in order for this to occur and to remove their concerns around sharing results that these protections needed to be put in place.

DR. KOENIG: I'm not opposed to any of these things. It's just that I don't think that they're the only thing, and I just am trying to counter that notion.

DR. McCABE: Judy?

DR. LEWIS: And I think we have to remember that just because we have a law prohibiting discrimination doesn't mean that it's going to go away, and that all that's going to do is give people recourse in case they were discriminated against, but basically the damage will already have been done. So that just because there's a law, I don't think we can let our -- you know, that's not the only way to go.

DR. McCABE: Okay, I would like to --

MS. BEARDSLEY: Can I have one more?

DR. McCABE: Okay. Kate, and then Pat.

MS. BEARDSLEY: One quick thing. I'm still back at trying to figure out what we can do to support this legislation. Can we write a letter to the President that the President can hand off to them?

DR. McCABE: No, we can write a letter to the Secretary.

MS. BEARDSLEY: Okay. Can we do that?

DR. McCABE: Or to Dr. Satcher. I'm not sure.

MS. BEARDSLEY: Saying we support this legislation and let him do what he wants?

MS. CARR: Outside the report.

MS. BEARDSLEY: Outside the report. I mean now.

MS. CARR: Yes.

DR. McCABE: So will you then empower Sarah and I to work on such a letter? We'll determine the protocol as to who it's to be addressed to. We will take a strong position and recognize that without anti-discrimination legislation, we will not be able to obtain the information we need to validate these tests.

Sarah?

MS. CARR: You're not endorsing any specific bill, right? You're just endorsing the importance of a legal --

MS. BEARDSLEY: Well, I think we're endorsing the President's position.

MS. CARR: Okay.

DR. McCABE: Well, he did it and --

MS. BEARDSLEY: I don't know that it's a bill. It's a position, though.

DR. McCABE: What we will do is we will determine the protocol on this. We will then write a strong letter recognizing the sense of the committee. We will e-mail it to everyone and request your response to it, but we've discussed the general content in this forum.

Pat?

MS. BARR: One IRB issue I think we've probably discussed, and I just want to be sure that we talk about it. To the extent that IRBs are involved in the process that reviews use of genetic tests in clinical practice, that those IRBs should be educated in the area of genetics and have genetic expertise.

DR. McCABE: That is something, I guess to the extent that we advise the Secretary and OPRR, falls within her office now. That is appropriate.

I think, though, that we need to again be cautious that we not say that if there is not genetic expertise in that community, that you can't do the research. So that we need to be cautious that it does not exclude, but we need to encourage genetic expertise within IRBs, and they need to seek this effectively.

MR. HILLBACK: Isn't that sort of a double standard? We're going to put tests through FDA, but we're

not going to push the IRBs to get genetically up to the appropriate level of knowledge? If we're going to be consistent, we're going to have to take a similar approach through IRBs, through the medical practice, through everything else, because if we're really going to uplift, we're going to have to uplift everywhere.

DR. McCABE: The problem is that what if there is only one geneticist at that university, if they're university-based, and that person would have to recuse themselves from that discussion.

MR. HILLBACK: Well, there are professional IRBs and the university can hire one.

DR. McCABE: Pat?

MS. BARR: I specifically spoke to the extent that IRBs are involved in the review of clinical practice, which is not often, as far as I know.

PARTICIPANT: Never.

MS. BARR: Okay. Well, then we don't have to worry about it. Then just take it out.

DR. McCABE: Okay, fine.

I think this is an issue, and I can tell you on my own university, we've got two IRBs that are relevant, and there's only person, and she is now on one IRB, reviewing for the other, soon to join the other, which is going to be an incredible burden, and since I requested her appointment and she's someone who I owe big because it happens to be someone else with the same last name –. This is the only person I could find who was willing to serve with any kind of genetic expertise on our IRB. It's not easy to do and there are, within academics, definite disincentives to being involved with IRBs.

And professional IRBs are not necessarily the panacea, and while they're approved by OPRR, they are criticized also, but it's something we need to address, and it has to do with increasing professional awareness about genetics.

I would like to move on now to next steps and discussion of other issues before everyone leaves, and that is one of the things we've talked about was patent. We've talked about the need for professional and public education, but we haven't discussed how we should go about doing that. I would like to put that on for the future about how we're going to achieve that.

And, then the other thing I would like to discuss, and especially because of his involvement in this I would ask Francis perhaps to provide us very briefly with some background about the discussions with OPRR.

DR. COLLINS: There is some information in the packet, and I trust people have looked at it, in terms of correspondence back and forth with Gary Ellis of OPRR.

And our interest in this was triggered by reading in the Washington Post that OPRR had taken away their approval for human subjects protocols in Richmond because of a number of issues, but the one that seemed particularly surprising was the issue of the twin study, wherein participants in this twin study were being asked questions about family history, and one of the parents of one of the twins got ahold of

the questionnaire and was offended by some of the questions that were being asked of a somewhat personal nature.

That person, who I gather has been fairly vocal -- in fact, I guess we were invited to have him come and speak to us, but we chose not to -- apparently convinced OPRR that this was in fact a circumstance that should not have happened without the IRB having had an explicit consideration of the benefits and risks of that kind of family history questioning.

That raised a lot of alarm bells because, of course, virtually all pedigree research that is being carried out around the world involves asking family histories of the participants in the research and, as far as I know, virtually in no circumstance do you go out and ask for informed consent from all of those relatives before you ask the proband about their medical history, and to begin to require that would seem like a very large departure from anything that OPRR has previously written and would be profoundly deadening in terms of the ability to carry out that kind of research.

So we wrote a letter, and Ed, I know you were involved in questioning this, and Child Health was as well.

If you read the letter that came back from Gary Ellis like three days ago, it is not all that reassuring.

It's a little hard to know what's going on in that letter.

But there is a paragraph in there -- I don't have it in front of me -- which I think says if you interpreted our comments on this to say that in this particular protocol consent should have been obtained from the relatives, then you might be right. Or something like that, and that we find very surprising.

Now again, we have not seen the specific protocol. Certainly, there's a suggestion that the questions being asked here were a particularly personal sort, but I would wonder whether they are so far outside the boundaries of what gets asked in many pedigree studies that that alone would justify this having been singled out.

So I think this is a pretty serious issue and I don't quite understand OPRR's position on this. Most people's view is that family history belongs to no single person, it is shared information in the family, and all the previous guidance, while pointing out that this is an issue, have not come to this same conclusion.

So this is all still a bit fresh and I'm not entirely sure exactly what OPRR's plans are as far as applying this same view in other circumstances or whether this is sort of one of a kind, but we thought this group ought to have a look at it.

DR. McCABE: We have some public documents in addition to the response to you, and I was impressed that very similar language appears there as well, and this had to do with the response to VCU, but it's basically the second paragraph, which cites the regulations defining a human subject and says that "By regulation, a living individual becomes a human subject when an investigator conducting research obtains identifiable private information about that living individual."

I think what I see as the issue here has to do with "private," because where it's communal information within a family, meaning held by more than one individual, then I think it's not private.

I'm concerned, and I know the American College of Medical Genetics is concerned, about this issue beyond the research, and that is that should this become a regulation that was true for all research protocols, it changes the nature of family history, and at a time when we're trying to increase awareness about genetics within the community, it could stifle our ability to obtain that information.

I would ask -- well, Pat, go ahead, please.

MS. BARR: I just want to provide an approach, because this issue came up with OPRR when we were trying to figure out how to do tissue banking, which clearly violated their notion of the regulations because we were storing tissue for research that was going to happen in the future and we could not let the subject know that the research was going to happen and what the research would be, and we definitely needed linked information.

So this is just strategic suggestions, and that is that the best way to go about dealing with this is to come up with a pretty clear guideline and system about how to do it alternatively that meets your needs, and then work with OPRR to convince them that this is an appropriate -- that it can fit within the context of the regulations in a reasonable and meaningful way.

It was not my experience when we did this other exercise, which is now being used, that they were ever really willing to jump up and down and say, "You're right," but they were willing to let it proceed.

DR. McCABE: Could I ask, since you have experience with this, Pat, if perhaps, and since Francis has been involved in this, and I would assume that communication is going to continue with OPRR, would you be willing, the two of you, to work on this, especially since you've had some success, at least in terms of endpoint, if not changing.

DR. COLLINS: Do you feel any impetus from the SACGT point of view to weigh in with a note of concern about this issue? Because that is something the committee could decide to do if you thought that was appropriate and we could draft something for you to look at.

DR. McCABE: Well, I think that's a strategic issue, and the issue is would it be better to figure out how to work with them, rather than get into a confrontational position that might cause a digging in of the heels, but I think we ought to discuss that within the committee.

DR. COLLINS: If it came to the point where it seemed as if it would be useful to have an opinion expressed from SACGT, I hope we could come back to you, Mr. Chairman, and offer that up and then you could see what you thought.

DR. McCABE: Well, is it the opinion of the SACGT that we ought to take on this issue?

MS. BARR: Yes.

DR. BURKE: Yes.

DR. McCABE: Okay. I think that's the answer, Francis, then, because we would certainly do what the committee felt was appropriate.

Joann?

DR. BOUGHMAN: Are we finished with this one, because I'd like to go back to the education issue for a just a moment and ask if in fact at our next meeting, or soon thereafter, we might be able to get a report from NCHPEG on their activities.

DR. McCABE: Yes, I think we'd ask earlier in the day or yesterday to get that information as part of our packet for the next meeting, so that we could look at that.

DR. BOUGHMAN: It doesn't matter whether it's oral. It may be written. It depends on the agenda, but I just think it needs to be available to us. We need to be updated.

DR. McCABE: Who is represented on NCHPEG? Is there someone on the committee? Mary? So maybe you could make a presentation to us about that, so that it would be both written and oral.

Francis?

DR. COLLINS: If I could add to that, there's also this meeting of Genetic Resources on the Web, or GROW, coming up March 27th-28th, which is an interrelated activity that is I think highly relevant to educational questions, and that could also be provided, information about that meeting.

DR. McCABE: If you could have your staff, then, provide us with that, and if you wanted to comment on that as well, Francis, or have someone from your staff.

Wylie?

DR. BURKE: And I could also comment on a HRSA-funded initiative called Genetics and Primary Care, which is bringing together a large advisory committee, sort of half genetics, half primary care, and talking about utilization of those materials, but also talking about that crucial issue of buy in. How do you make genetics relevant to primary care?

DR. McCABE: And it makes me think also, we talked about GeneTest and GeneClinics, and since it is on the Web and the Web is accessible by everyone, whether we should also invite Dr. Pagan, because there might be some educational opportunities there.

But what is people's thoughts on that?

PARTICIPANT: It's a good idea.

DR. McCABE: Okay, and Judy?

DR. LEWIS: And I think the last piece that goes with that is Healthy People 2010 and looking at what the initiatives are for genetics and genetic education in there, so that we're working in concert with that.

DR. COLLINS: There aren't any.

DR. McCABE: I think I heard that there was one genetic issue raised. I don't remember what it was.

DR. COLLINS: There was? I couldn't find it.

DR. McCABE: David?

DR. FEIGAL: Another topic for us to consider. I think we've been talking mostly about the products that focus on a specific disease, but the type of product we're increasingly being asked to think about is the chip that tests for 10,000 conditions simultaneously, and I think we need to think about that. Some of them are actually claiming not even to be medical. It's just information. I think these actually pose another whole challenge to think about the paradigm for using these.

DR. McCABE: Barbara?

DR. KOENIG: I just want to second that, because that was on my list of sort of leftover things that I'm concerned about. We also had public comments on the issue, so it's in the document. We had some oral testimony about the issue of multiplex testing, and I think these do raise very considerable issues.

And, also, it gets us back to the issue of the non-medical. You know, the tests that are allegedly for something else, you know pure information, whatever.

DR. McCABE: We have on our agenda to discuss the status of the OPRR situation at the next meeting, to bring in a number of issues about education of professionals and the public. Would it be possible, would it be acceptable -- and then the other thing we'll have to do in May is be finalizing the document with the feedback that we've gotten. So would it be acceptable to postpone that to the meeting after the May meeting? The chip.

DR. KOENIG: Well, sure, unless that there is some need -- if we're going to talk about a why a coordinating, or a non-coordinating coordinating, whatever we're calling it, one justification I think for that is the fact that this technology is on the horizon, and I don't know if it's worth saying that now. Maybe we haven't had a chance to consider that yet, but --

DR. McCABE: Wylie?

DR. BURKE: I'd add to that that I suspect any, even fairly brief, discussion will lead us to the idea that a chip test is a high scrutiny test.

DR. McCABE: Well, why don't we put on a discussion of chip technology at the next meeting? I don't know that we need a presentation. I think that we have some feel for that, but I'll assess whether we need that.

Francis?

DR. COLLINS: Could we just amend that to be high throughput multiplex genotyping? Because it's not all chips. There are other things out there that do this and maybe even will do it better.

DR. McCABE: Right. So we will have a discussion of high throughput multiplex genotyping at –. Did I get them in the right order? At the next meeting. If anyone feels strongly that there is someone who should give us a presentation, it would be fairly brief. I think a lot of us are familiar with those issues, but

if you feel we need a presentation, let Sarah or I know.

Other issues? Barbara.

DR. KOENIG: I don't think we've done justice to the pharmacogenomics issues and how they're separate, and the oversight of the whole issue of how SNP data will be maintained and whether there are separate privacy issues, all those kinds of things. And I don't have a solution.

DR. McCABE: Do we want to discuss that at the next meeting or could we ask for a representative of the pharmacogenomics community to come to the meeting after the May meeting?

MS. BARR: I wonder if we could actually even ask them for a written something to us as it's done on their perception of where they fit into oversight. Since they were connecting the test to drug, I'm just wondering what their sensibility is about whether they come under the rubric or they don't. I'd be very interested in knowing.

DR. McCABE: Do we want to take it beyond Glaxo? We've had two presentations from Glaxo. So I think maybe at the next meeting perhaps we could identify additional entities and then consider for a future meeting some presentations, plural, and further discussion.

Wylie?

DR. BURKE: And I was going to say, I think we need to defer it to the following meeting because we need to do justice to it. I think we need to have a detailed discussion.

DR. McCABE: Francis, did you have something to add on that?

DR. COLLINS: No, I agree completely, and there are other folks besides Glaxo that I think could be very useful presenters. The whole SNPs Consortium, with its 10 pharma companies, would have an interest in this.

DR. McCABE: And we've had Allen Buchanan speak to us before. He was involved with the presentation, but we can think of him as a potential discussant. So at the next time, let's try and identify who the players are and get out a request to them.

Barbara?

DR. KOENIG: And we've done the same thing with patents, because I think maybe a presenter on patents would actually be useful at some point.

DR. McCABE: Yes, but I don't know if we're going to be able -- Sarah reminds me we're having the consultation with NBAC in May with about what they're doing regarding patents and that will help inform us.

Yes?

MS. BARR: Someone mentioned a very short time frame on comment, though, today and I just

wondered what that was about. There's a meeting and then --

DR. COLLINS: So, the meeting is next Thursday, March the 2nd. The deadline for comments to the PTO's Federal Register posting is March 22nd, so it's coming up very fast, and the hope would be that they would hear from the community. As was pointed out yesterday, what's posted in the Federal Register is pretty tough sledding to get through, and I hope that the meeting, which ACMG and Vanderbilt are putting on next Thursday, will clarify some of those ambiguities and inspire some people to respond.

DR. McCABE: Our problem, if you're indicating that you think that we should be responding, it's going to be very hard to do that because we would have to have another meeting before the deadline.

DR. BURKE: And I just want to add, I think it's unrealistic for us to respond as a committee, but is there any possibility that there will be some effort to disseminate, maybe via the Web, maybe via e-mail, thoughts about the meeting and thoughts about what comes out of the meeting?

DR. COLLINS: Yes.

DR. BURKE: Because certainly I think it would be helpful for all of us who are not going to attend that meeting to receive some feedback prior to March 22nd, so we can make decisions about whether we want to respond as individuals.

DR. COLLINS: We can do that.

DR. McCABE: Yes, but be very clear that if you respond, you're responding as an individual and not as a representative of this committee.

Kathy Hudson had already told Sarah that she would get Sarah the information, and Sarah will blast it out to us.

DR. COLLINS: A particularly interesting part of that meeting will be the unveiling by the PTO of these examples that they intend to use in instructing their own patent examiners about what to allow and what not to allow. Nobody's seen those yet, and those I think will be worthy of study. We can also send around to you some correspondence with the PTO and NIH which I think also lays out some of the issues.

DR. McCABE: I think that one of the things that is very clear is that there has been some interest in the White House about this issue.

DR. COLLINS: Oh, yes.

DR. McCABE: And given our reporting structure, you know, it's something we should take up while the current administration is intact.

DR. COLLINS: Hear, hear.

DR. McCABE: Other issues, discussion, comments?

(No response.)

DR. McCABE: If not, I want to thank all of you. I think we've come a long way during this meeting. I think that we will have a report that will contribute. I do not think it will be an endpoint, but a takeoff point for future discussion.

I'm pleased that the FDA is willing to consider some flexible approaches to these issues, because I think we're all concerned that they could be a bottleneck, a genetic bottleneck, as it were.

But thank all of you for your candid discussion during this meeting. Have a safe trip home.

(Whereupon, at 5:20 p.m., the meeting was adjourned.)