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ON GENETIC TESTING

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P R O C E E D I N G S [9:12 a.m.]

Chairman's Remarks

DR. MC CABE: Good morning, everyone. I especially want to welcome Pat Barr, who is on the phone with us. Pat?

MS. BARR: Yes.

DR. MC CABE: Thank you for joining us by phone. We are glad to have you and appreciate your involvement.

Welcome to the 7th meeting of the Secretary's Advisory Committee on Genetic Testing. The public was notified about this meeting through an announcement in the Federal Register on October 5th and a posting on the SACGT's web site.

We appreciate the public's interest in our work and welcome hearing from members of the public in attendance during the comment periods this afternoon and tomorrow morning. We have several individuals who have registered for that. Anyone who would like to speak, please just let Sarah or one of her staff know so that we can get you on the list.

At our last meeting in August and with the help of a working group composed of SACGT members and ad hoc experts, we reached agreement on a framework for classifying genetic tests and since then have drafted a report based on the conclusions reached at our meeting.

At the end of September, we submitted this proposed framework as an addendum to our longer report enhancing oversight of genetic tests, which was submitted in July. The addendum is included at Tab 2 in your briefing book.

Subsequent to our last meeting, there has been further discussion of the methodology, particularly the first criterion on test volume. We emphasize that the methodology is a work in progress that requires further refinement and we have been encouraged by the additional comments and discussion that the proposed methodology has stimulated.

At this meeting, we will be discussing the methodology again in the context of the report of the Rare Disease Testing Group and presentations by the CDC and the FDA. I would anticipate that this will be a significant portion of the discussions at the end of the day.

In August, we also had an extended discussion of current and emerging issues in genetic testing. From that discussion, we identified five priority issue areas and established teams and work groups, which were subsequently augmented with ad hoc experts to begin a focused study of the issues.

I want to commend the efforts of all five work group chairs and members. I know that since August, you have devoted a great deal of time to advancing the group's agenda and we are looking forward to hearing about and discussing your progress and future directions.

As productive as I know these effects have been, I wanted to be sure that we aren't trying to do too much at once. We all agreed in August that these five issue areas were important and warranted attention and that we wanted to make a contribution in many areas.

Doing justice to the issues requires in-depth consideration by the Committee as a whole and I think we may need to think about whether we might be spreading ourselves too thinly. In this regard, I want to remind us of something that Dr. Collins said at the last meeting. He identified several criteria that might be useful in setting SACGT priorities.

He suggested that we concentrate on those issues that are directly related to our mandate and core responsibility of ensuring that genetic testing is responsibly carried out to the benefit of the public. Francis suggested that we avoid issues that other groups might be better equipped to address and focus on those that take advantage of our role and position in advising the Secretary of HHS.

With these criteria in mind, I would like to suggest that during each group discussion we give some thought to priorities within the group and tomorrow we take some time at the end of the day to consider our overarching priorities across the five groups.

I would like us to be sure that we have set realistic, achievable goals and that we are able to generate concrete work products. In addition to reports from the five groups, we will also hear presentations suggested by the membership on three important topics related to the priority areas.

FDA and Federal Trade Commission regulations governing the labeling, promotion and advertising of medical devices, reimbursement for genetic testing services and genetic testing, and informed consent issues in clinical research settings.

Before we get underway, I want to take another moment to mention some important outreach meetings that have occurred since our last meeting. I briefed Dr. Satcher about our oversight report in late August and last month, with the CDC senior leadership, the administrator of HRSA and the acting administrator of HCFA. Three more agency briefings with FDA, AHRQ, and the Office for Human Research Protections are scheduled next week.

You will recall that I briefed the NIH leadership before our last meeting I also participated in several important public outreach efforts, involving meetings at the American Society of Human Genetics and the American College of Medical Genetics Foundation.

Other members have been active in outreach efforts as well. Dr. Lewis served on an expert panel for a HRSA-sponsored meeting on genetics and nursing and an ethics panel at the annual meeting of the Virginia Biotechnology Association.

Dr. Boughman, as you will hear later today during her presentation, has consulted with a number of groups to gather input on education issues. We may hear some of these and other activities during the group reports.

I also want to take a moment to thank Sarah Carr and her staff for their tireless efforts for the SACGT. This has been a very busy time with submission of the Committee's report and the addendum and then all of the briefings and presentations. They are really to be commended for the work that they have put in on this. Thank you very much.

This concludes my opening remarks and before we get started, Sarah will review the conflict of interest rules with us.

Conflict of Interest Guidance

MS. CARR: I am just going to remind you that during your service in our Committee meetings you are considered special government employees and you have to adhere to the rules of conduct that govern government employees. These rules are set out in a document called the Standards of Ethical Conduct for Employees of the Executive Branch. It is something that you all received when you signed up for this service.

I am just going to mention one rule, which I usually do and it is a very important one. It relates to conflicts of interest.

As you know, before each meeting of the Committee, you are asked to provide us with a great deal of information about your personal, professional, and financial interests. We use this information as the basis for assessing real or potential conflicts of interest or even the appearance of such conflicts that could compromise your ability to be objective in giving advice during meetings of the Committee.

If you are found to have conflicts, waivers can be granted because the need for your advice outweighs the potential for a conflict of interest created by your interests.

Most of you have granted waivers for general matters. If a specific issue comes up during a meeting that could affect your interest specifically, you have to excuse yourself from the room, from the deliberation, and from participating in the discussion.

There are lots of other rules and I want you to be familiar with them, but that is an especially important one. If you have any questions about that rule or any others, please let me know.

Thank you.

DR. MC CABE: Thank you, Sarah.

Now we are going to hear from Dr. Wylie Burke for a progress report from the Data Team and following her report, Wylie will lead a group discussion of the Team's progress and its next steps.

Report from the SACGT Data Team

DR. BURKE: The roster of the SACGT Data Team is shown here. Ann Boldt, Mark Greene from NIH, Marta Guinn from CDC, Cecilia Hinkel from HCFA, David Lanier from AHRQ, Marie Mann from HRSA, Vicky Wittemore as an ad hoc member from the Genetic Alliance, Pat Barr, Maria Chan from FDA, Steve Gutman from FDA, Elliott Hillback, Muin Khoury from CDC, Penny Manasco and Reed Tuckson.

This is in your book but let me just briefly show you the issues and time table that we were assigned and I will make a couple of comments because, as we went through our conversation, some of the issues became a little clarified and I think changed at least how we perceived our mission a little bit.

So, before this meeting and in preparation for this meeting, the expectation was that we would generate a list of pre- and post-test information elements. So, the idea has always been that test labeling is a very important part of the outcome of the regulatory process of pre-market review.

So, our task was to come up with a list of things that were important to know pre- and post-test. As we got into our discussion and really focused on where our attention was, which was really what kind of data should be available about a test as part of pre-market review of that test, it became clear that pre- and post-test is a little bit of an artificial distinction.

So, what will become clear as I go through our table of elements is that what we felt we had to do was come up with a list of the pieces of information one would consider putting together as part of a pre-market review of a test. What kind of information should you have when it comes to pre-market review, who should provide it.

As we went through that, that led to some implications for what kind of data you would hope to gather in post-market review or in post-market use. But it didn't fall out simply as pre- and post-test.

Then we were asked to identify methods available for determining the volume of test use, the potential of these methods to serve as a mechanism for that first step in our test classification. I know that this will come up in other reports as well and I will just get straight to the point on that. We couldn't come up with a good method for measuring test volume.

We were not convinced that there is any reliable unambiguous method that everybody is going to agree to that says "yes," this is test volume. So, we think that that has to be a point of discussion and we know that that will, as I say, come up in a couple of other reports and, therefore, will be a point of discussion.

Then, obviously, our work subsequent to this meeting, as outlined here, will focus considerably on data and collection methods. I think those data collection methods will focus a lot on what kind of data comes after a test comes to market. So, that is what we will be working on.

We did ask our membership of the Data Team to let us know about anybody that might be an appropriate organization to review; that is, in terms of reviewing what we came up with in draft form. We tried to be as inclusive as we could and basically encourage people who had participated in our team discussions to disseminate our draft widely and give us feedback. We have a little feedback so far. I am assuming more will be forthcoming.

So, the main product of our discussions then up to this point has been discussions about what kind of information do you want to have about a genetic test. Once you have figured out what kind of information you want to have, what pieces of that information really have to be there in pre-market review.

So, I am going to go through the list of items. You also have this in your notebooks. This is just a table and the first product of our discussions is that list of items. So,

the list represents -- what you see in Column 1 under "Elements" -- those pieces of information we thought were important about a test.

As I go through this list, I am going to refer to the definition and also the source of the information. A lot of our conversation was around source of information on a particular data element. That conversation led us to some conclusions about what laboratories should offer pre-market and what is unreasonable to ask laboratories to offer pre-market with some of the implications.

So, first of all, the first element, what is the purpose of the test. So, we thought it was appropriate to be able to state for any test what that test is and what are the settings in which that test will be used. An example, is it a diagnostic test, is it a predictive test, is it a carrier test, is it going to be used for prenatal testing, is it going to be used for screening, et cetera?

Each category of tests used represents a different test for the purposes of pre-market review. We felt that you had to come to that conclusion. I think it is consistent with conversations we have had before because other test properties potentially change with different uses of the test. It seems pretty clear that the laboratory needs to define the purpose of the test for which the pre-market approval is sought; that is, the lab says this is a test to diagnose such and such.

But when we think about purpose of tests, we realize that there really is an evolution of practice standards that has to happen separate from the lab offering the test. That is, there is an evolution in thinking on the part of the clinical community, the health policy community about when and where such a test might be used, how it should be used, what kind of services should accompany that test. Sort of a development of clinical practice standards that has to happen over time.

It is not reasonable nor even desirable to ask a lab to set specifications for those aspects of the test. That gets us back then to some advice we have basically had, which I hope I am interpreting correctly, about what FDA would normally require in a pre-market review, which

is the tests should have a purpose and that purpose should represent a plausible clinical use of the test. But that is really the extent to which the pre-market review can expect a purpose.

Clinical condition for which the test is done. Clearly, one would want to specify fairly clearly what the clinical condition is in terms of prevalence, its clinical manifestations, its prognosis, et cetera.

What we think is reasonable to expect the lab to provide in pre-market review is to specify the condition as part of its description of the plausible use of the test. It can reference literature. That is, it isn't necessarily expected to provide its own original data.

Again, there will be a development of practice standards over time in terms of the use of that test vis-a-vis that health condition.

Third element, definition of the test and by that we mean the specific laboratory measurements, which are to be undertaken. Clearly, that is the responsibility of the laboratory to clearly define what its test is.

Very related to that, its analytic validity, the accuracy with which the laboratory measurement identifies a specific genetic alteration. So, we are talking about genetic tests. The assumption is there is some genetic difference that is being measured and the lab should be able to provide very specific information that is related to its own assay regarding the accuracy with which that assay measures that genetic alteration, but that it is acceptable to use published literature on expected test performance when that is available.

Clinical validity. So, our definition, accuracy with which the laboratory measurement predicts the presence or absence of the clinical condition. We did try to separate out what we mean by clinical validity for a diagnostic versus a predictive test. For diagnostic tests, for prenatal tests, for carrier tests, the accuracy can be expressed as sensitivity, specificity, positive and negative predictive value.

But for predictive tests, although we try and use those same terms just for clarity, we wanted to make sure that we were stating that with a predictive test, what you are doing is

estimating the expressivity, which is the range of phenotypes that might be associated with a positive test and estimating age-related penetrants. So, it has always, I think, been hard to apply positive and negative predictive value to a predictive test. We are trying to make that distinction here, including acknowledging that particularly in early test development, this is often an estimate.

In the end when you have got all the data you want, it is a probability statement. So, laboratory defines clinical validity as relative to the proposed used of the test based either on its own data or published literature. We are referring here to conversations that we have had in this Committee that it is understood that often there will be reference to published data.

The quality of that data is a reasonable focus for pre-market review. Most important, that the information that is provided about clinical validity includes a statement about its limitations. So, if the data only came from high-risk families about the limitations, it implies that what we know about the test only is used in high risk families. The absence of population data would be important.

And, again, what we know about clinical validity will clearly evolve. So, this is probably one of the most important places to note that post-market there will be a process of accumulating information about clinical validity. To some extent you only accumulate a large population to do that after the test has become available and on the market.

We assumed that the evolution of information is not something that is the sole responsibility of the laboratory but really is part of something that occurs and is done by clinical/health policy communities.

Price of tests/reimbursement. We actually had put reimbursement first as the element that we wanted to know about and then we realized that if you are asking the lab to provide information pre-market, really all you can ask is what price is going to be charged for that test.

Reimbursement policies, again, are going to be a matter of guideline development and setting policy by different health payers. The lab doesn't really have control over that. That may change over time.

Finally, clinical utility. Interventions available to people with positive test results, either for treatment or for prevention of disease, level of evidence concerning their efficacy, a very important part of that, any other potential benefits of either a positive test result or a negative test result that influence health outcomes.

The most important conclusion that we took from our discussions was proof of clinical utility is not an element you would request as part of pre-market review. It is not part of what is currently required by FDA pre-market review. The data to prove health outcomes and to establish the efficacy of interventions for the interventions given to test positive people are not pieces that reasonably could be expected to be provided by a lab.

So, we get back to the statement we had about purpose of test, which is it is expected that a lab can state a purpose of a test and that purpose should include a plausible use of the test for clinical benefit. But proof of utility in terms of measurable health outcomes and descriptions of the level of evidence about the efficacy of interventions for test positive people is not a reasonable thing to expect from pre-market review.

Obviously, that is a tremendously important element of a test, of knowing about a test and valuing a test and, again, puts us very critically into how do you gather the information, analyze it and disseminate it post-market.

So, those are the discussions that the committee had. Other Data Team members please speak up if there are pieces that I have adequately represented. I think we are open for discussion.

Discussion

DR. MC CABE: Are there comments from any of the other members of this team about the discussions?

MR. HILLBACK: I would just say I think Wylie did a great job and we did get some feedback from a couple of the labs and the lab directors to try to get down into the details. So, I think this was a consensus beyond just the working group. We got some other folks to take a look here and there and give us some feedback. So, we would like to hear a response now.

DR. MC CABE: Other comments from members of the working group?

[There was no response.]

Not being a member of the working group, I thought this was quite interesting when I saw it because one of the things that I have been thinking about a lot as I have been going around and doing the briefings is what was kind of the kernel of what we have been discussing over the last year and what was really the kernel of our recommendations.

One of those to me was this concept of education of the public and the professionals about what we know about a test and what we don't know about a test. And almost thinking of how that would be, it really gets down to labeling and all of those label inserts that become the PDR and thinking about doing something like that for the genetic tests. To me, this looked like it was beginning to have the elements of that kind of brief but very informative information.

I don't know if that was something that you talked explicitly about but perhaps you could inform us about that.

DR. BURKE: Yes, I can just comment actually and I should have made the comment -- and Steve may want to elaborate on it, that we did get some feedback from Steve based on review of our first draft and some of those points were made that there needs to be careful attention, that that is the fundamental purpose of this kind of summary statement and,

therefore, that appropriate reading level needs to be taken into account, perhaps adding a section called "Frequently Asked Questions."

There was also a suggestion about making explicit what the implications of test results would be for family members. Within all of that, how does reach the end user.

Do you want to elaborate on that?

DR. GUTMAN: Actually I do. Actually at the round table that we had about a week and a half ago, there was a suggestion. I don't know if it has percolated to Wylie yet or not, but a suggestion that there be consideration to, either within the context of this template or perhaps a parallel template, making a patient user version.

If you look at the NCI trials, for example, there will always be a professional and then there will be a patient version with the same information. An informed patient has access to both or I suppose an informed health care provider has access to both. But they are written a little differently. So, one possibility would actually have two versions of this.

DR. MC CABE: Yes, Muin.

DR. KHOURY: I would just like to reiterate what Wylie said earlier about the potential overlap between the pre- and post-market phase of data collection. You will hear from me a little bit later on today, but it struck me as we sat down last week to discuss the data template for the post-market phase, which is sort of what CDC is currently doing right now, that some of these elements that Wylie presented, which are now being put into the pre-market phase and review by the FDA, will come back and, obviously, be modified as the state of knowledge gets filled in with more data, especially on the clinical side of things.

I think those two processes can move synergistically and you will hear from me a bit later on during the day.

DR. BURKE: I think another point that comes out of both Steve's and Muin's comments and is not something we explicitly dealt with because it wasn't the task at hand is how

do you put together the pieces of information that derive from evolving practice standards with the pieces of information that came from pre-market review.

We have said all along that post-market data issues are not just collection analysis, but also dissemination. It may be a very important part of the oversight process, somewhat separate from pre-market review, to make sure that there is a mechanism for getting that information out.

DR. COLLINS: Could you just clarify, Wylie, in terms of the audience for this particular table, which I think is a very thoughtful document and does hit on all the important elements? Is this partly intended to guide the FDA in their decision-making or is it also intended to be an enumeration of what physicians or other test providers would want to be sure they knew about before offering the test and is it also, as Ed was saying, sort of part of the package insert, the labeling, that tells the patient who is potentially going to get tested what this test is all about.

Is it trying to do all those things?

DR. BURKE: I think if the test does what it should do, it should do all of those things. In other words, to some extent, I think all of those are separate issues, but there ought to be a single uniform agreement about what the data is.

Now, one of the reasons why we did what we did in Column 3 is that once you have got your uniform list, and this one may not be there yet, but once it is exactly where we want it, then it seems to me you have to be realistic about the fact that different assignments go to different people. So some elements, the lab just has to do it, that the test offer has to provide it and others, professional organizations are tremendously important in developing.

But I think it is a good thing to have a single list that we all work from.

MR. HILLBACK: Francis, actually just partially in response to your comment too, we took this to several of the lab directors at Genzyme in the genetic testing business and said, how does this look to you, and the interesting comment I got back was, well, as far as we

are concerned, we have this information. We use it ourselves. We don't publicize it all, which goes back to a point Muin has made before and others have made before.

But they had almost no edits to where we had gotten without their input and I think what made them more comfortable was, as Wylie explained, the recognition that in certain cases, it was outside groups when it came to practice standards and clinical utility that had to somehow get involved. So, the laboratorians that I talked to, and there are lots of laboratorians, so I only did a small sample, were quite comfortable that this was a list that they had to do in order to do a test anyway and, therefore, it made a lot of sense.

DR. LEWIS: The thing that makes the most sense to me about this is the ability to get the test on the market for its intended use, but then to be able to develop practice standards. I think that is a really important piece. For me the thing that would be important for consumers is to have a sense of how those practice standards are developed because this is what is really -- we have been talking about off-label use -- this is how that gets developed into becoming current practice.

I want to make sure that we were collecting data to make sure that those practices were as reliable and valid as the original one, but I like the way you have set this up so that it doesn't stop people, but yet, consumers will have a sense of what is the intended use and the fact that this is moving further.

DR. CHARACHE: Judy is on my wave length, but I am going to also point out a concern with the deviation from intended use because I think this is where the test review and oversight interdigitates with the laboratory review and oversight.

This is one of the areas that was of greatest concern to CLIAC and I actually had it on the slide, that all larger companies will come in with a very limited intended use so they can get their product through the market, but then we will know ahead of time that they were going to expand it.

So, everyone will come in with a diagnostic, rather than a predictive because it lowers the scrutiny. But they intend it to be used as predictive. This then becomes a very major challenge because the FDA has never addressed the issue of off-label use and really can't.

So, I think this brings us into the question of protection of the public because I am very sure we are going to see everything come in as a diagnostic and, yet, maybe intended by the manufacturer to be used for not only Alzheimer's diagnosis, but also prediction. So, I think this is an area that has to be thought through very carefully. It is both a strength, as Judy has pointed out, but it is a very severe limitation as we can anticipate the usage of that approach.

DR. BURKE: I can just comment -- Steve may have comments, too -- that off-label use has come up a lot, obviously, in our conversations and it did come up in the Data Team's conversations. As you say, to some extent, one cannot prevent off-label use once a test has come to market.

The comment I think that we could make vis-a-vis this list of test properties is that at least if there is a set template, everybody knows that there is a set template and there is agreement about what is in that set template, it maybe becomes a piece of information that is used fairly commonly. You can then insert appropriate statements. You can assert appropriate caveats particularly if you are concerned about the potential for off-label use, that might include the safety and efficacy of this test is not known in certain circumstances or things of this kind.

DR. CHARACHE: I think this is why I said this is where it interdigitates with oversight of laboratory practice as we think through how one would have a checklist, which says, are we capturing intended use and is there anything else we should know about it as we go along.

DR. BURKE: I agree.

DR. LANIER: Wylie, we discussed this briefly in our group meetings, but I am a little bit concerned that this information will be put together in a pre-marketing phase and then over time it may change.

Can we have a little discussion about updating this information because it seems to me that this would be a repository of information that, obviously, could be refined over time and needed, I think, to consider whose responsibility it is to update?

DR. BURKE: Yes. I think that is a good point and as you say we didn't really discuss this in-depth. So, I think probably we should just throw this out as a discussion point now.

DR. KHOURY: That is the whole issue here because the information that comes in the pre-market phase will change almost the day after or if not the week after. That is why we need this pre-/post-market analysis and coordinated effort to put into an easily found database, if you will, or source of information what we know and what we don't know, using the famous Elliott Hillback's statement, and that is what we really are trying to do from the CDC perspective, trying to put those databases together, working with all the other agencies in order to have a place of information people will feel comfortable using for that evolving piece of knowledge.

One other piece I wanted to say before I forget, the off-label use is so important, but I am not sure we are going to solve it here because it transcends genetics. I mean, it is all medicine and health care and every other aspect. All we can do is make sure to tell people what this product is going to be used for and what Pat was saying about the laboratory testing process being informed and having checklists and also being part of the package for surveillance, because as we begin to collect information on who is being tested and the magnitude of testing, we can collect the information about the appropriateness or the indication of use and then come back and say, well, half of the utilization of that test was not for the intended use.

That kind of information can become a tremendous post-market surveillance tool to provide the right policies for both regulatory and professional organization development policies.

MS. DAVIDSON: I just want to follow up on Muin’s comments. Actually, I think you said pretty much what I was going to say but just to emphasize from the consumer's

perspective the harm potentially that bad information, out-of-date information can cause and I think particularly as we get into an accelerated pace with the development of information, that being sure that we have adequate resources and we know who is going to be part of that process so that someone who is taking a test really has the benefit not only of the best reviewed test, but also the information that goes along with it because I think just to follow up your comments, Wylie, I think that while I may have come to this thinking much more in terms of FDA review, I think that as more information, the more that we can really empower people to have a better understanding of the process that they are going through, that that adds a whole level of quality through testing that is almost impossible at this point to measure, but it is really a place we need to put our effort.

DR. MC CABE: Wylie, did you want to respond to that?

DR. BURKE: I actually just wanted to throw out that there may be two things that we want to think about in terms of developing these summaries. One is that they are always dated so that anybody using it knows when that information was generated and the other is that it may be reasonable -- I will raise this as a question, but it may be reasonable to say that those pieces of information the lab was required to provide in pre-market review should be the responsibility of labs to update.

What I think you get to very quickly, though, is a hundred different labs might be providing a test and presumably both on the lab side, that is, those pieces that really are the lab's responsibility, and on the clinical practice standard side, sort of the larger community. It might well be that this process will go best if there is some development of consensus, some cooperative efforts to work together on the updating process.

DR. LEWIS: I think this moving target piece is a piece that I wanted to address in terms of the fact that the approval is done at a point in time, that knowledge is not a static thing and it keeps going. I am not sure we want to get into a every month we are going to review this again type of thing, but it seems to me that the whole idea is that this is a developmental

process. I am not sure "iterative" is the right word this morning yet, but it is a developmental process in terms of knowledge keeps developing and everyday we know more. It becomes really hard to say to the clinician in practice and the patient receiving the test, this is what we know today, this is what we don't know today.

I think that more and more as people are using the Internet as a source for health care information, updating becomes reasonable and possible and having people know what the best knowledge is and that a test has been approved for Use A. We are using it now and I agree with Pat, maybe I am a little less cynical, but I am not sure that people are going to have a use right in their back pocket.

Let's give people the benefit of the doubt that as new uses develop, and they may, but as new uses develop, I think what we need to do is just make sure that people have current data and up-to-date information and that we just need to make sure that there is truth in advertising.

MR. HILLBACK: I totally agree and I think that maybe the way to sit back and think about this is to say we want to establish some principles about what information ought to be there at any point in time for any tests. So, if you go and get pre-market approval for a diagnostic and the world changes and now there are additional uses as a predictive test, the physician ought to say, well, I saw your chart for the diagnostic version. Now, you are offering this test for a predictive use or I want to use it -- I, the physician -- in my clinical practice would like to use it as a predictive test. Where is the data?

So, I think if we can think of this as setting a standard of the basic knowledge that ought to be available and ought to be updated on some regular basis so that as we educate the users more, second, another subcommittee later on, that they know to ask for this and they expect it. I think then we create a real honest interchange between the laboratory and the clinical practice folks.

So, it becomes a minimally accepted standard that you have to have this information. I think that goes to a number of the comments, whether it is Mary's or Pat's or Judy's, that we have to get people used to the fact that this ought to be there. If it isn't there, we ought to ask why isn't it there. Why don't I know this? Why won't you tell me?

MS. BARR: We might want some incentives out there for the research to happen. I mean, that is not what usually happens now. We leave it to academic interests or the market, but some of this is about facilitating the data collection, not just saying the data should be out there. At some point I think we should think about that.

DR. MC CABE: Muin, do you want to respond to that?

Thanks, Pat.

DR. KHOURY: Thank you. That is a great point actually. I think one of the biggest incentives or there are several lines of attack on this. One, by displaying and updating what we know and what we don't know, those tests that are being used are not reimbursed for some purposes or could be -- we will discuss this a little bit later -- we create a de facto incentive for both government agencies to fund research by NIH and CDC and others as well as industry because if we follow the ground rules of saying, okay, here is the data we want, here is the format we want it in and we go find what we can find and come back and have a bunch of empty boxes and that would become your truth in advertising and then you put the test out there and people will see immediately there are major holes. So, they can't get reimbursed for that test. I mean, the labs might turn them away. So, hopefully, by bringing the public and private sector together, you will create the incentive of further data collection, with the understanding that this is the data we want. So, it basically becomes a -- you close the loop. You close the gap of the lack of information, which as you begin to set on this course of action, you will have gaps of information in the beginning.

So, it becomes less of a regulatory process but more of an incentive for the private sector to sell their products, for academia to do the research, and for the federal funding

agencies to fund those consortias and collaborative efforts. So, I am hopeful that this would be a major adjunct to pure regulations that would drive the wagon.

DR. MC CABE: I think that is an important point and one of our roles is to advise the Secretary not only about recommendations regarding oversight and these other issues, but also about areas of research that we determine. So, I think that is a good point to remember for your report then, Wylie.

DR. CHARACHE: Just returning to the thought of who needs the data that is being produced, it is clearly the people who order the test that have to know what information there is about that test and how it is proposed to be used, whether or not they choose to go off-label. One of the challenges that we have now is that all of the information that is in that package labeling that defines what has not been proven and what has been proven remains in the laboratory.

I think we have to be thinking as we come up with this data and want to be sure that off-label use is appropriate and not inappropriate, that it becomes key that we find a way of providing this information to those who ordered the test in appropriate format.

DR. BURKE: I think that is a tremendously important point. It follows up on Elliott's point that we need to promote the development of a good informative document that test users then expect to have, expect to see, and question if it is not there. I would say not just the doc ordering the test, but the patient receiving the test in an appropriate worded document.

That strikes me as a tremendously important focus for education, that tests can be summarized, that here is why these are the pieces that you want when you look at a test summary and look for it. Here is how to interpret this document, et cetera.

MS. BOLDT: As I am listening to our conversations, too, it is interesting that we say that after we have the data we are going to be able to establish clinical guidelines, but in some ways we need that up front a little bit because without ordering and using the test appropriately, we are not going to get good data.

So, in some ways it just underscores the need for genetic education and counseling to accompany these tests, especially before we have this data to establish the guidelines. So, it is kind of a cart before the horse, too.

DR. MC CABE: Steve Gutman is out of the room, but I just wondering if Joann as liaison with the FDA MDAC might know whether -- what is periodicity of FDA review? Is that built into any of the reviews and then also about warning regarding off-label use.

My understanding is that the FDA can include in the labeling warnings if they feel those are indicated, but I was wondering about clarification of that.

DR. BOUGHMAN: The periodicity is not a routine past of the review process. In fact, the company or source of the test or whatever would request a different review, but it is at the request of -- as Dr. Gutman has indicated, the FDA is very, very keen and pays a great deal of attention to the labeling process and, therefore, does feel strongly about including warnings when appropriate.

However, I guess the mantra more has to do with clarity in the labeling itself on the proposed and approved use of -- even in the absence of warning statements in boxes or whatever and during the review process in fact there may be suggestions made about the format of the labeling in such a way that if there are issues or concerns, they can be addressed and noted in format as well.

One of the things I have been thinking of while we are going through this discussion is in the manner of creating an ongoing and evolving understanding on the part of the laboratorians, the clinicians requesting the test, and any labeling that goes to individuals, I am wondering if we might not consider the possibility anyway of a very clear, straightforward definition of predictive tests and other tests so that, in fact, that phrase becomes knowledge that all of us share, so that then when in labeling processes later, in every labeling process, the word "predictive" is used, there is an understanding.

That comes back to Pat Charache's comment earlier that it would be more easily recognized in the future when somebody is moving to an off-label predictive use. I am just wondering if in every label there might be certain phrases that are routinely used.

DR. BURKE: I actually think the definition of a predictive test is a crucial thing for us to discuss and I don't think it is going to be simple. I think the simple way to do a predictive test would be to say a test done to predict likelihood of disease in a person who does not currently have the disease.

The problem is that you then run into the question of what in genetics terms is awful the distinction between presymptomatic and predictive. That is, to what extent is it fair to call a test predictive if there is a virtual certainty that the patient will develop the disease. They just don't have it yet, as opposed to the test that I think we are all certain is predictive, which is the test that identifies increased risk.

The example I would give is PKU testing. I don't think we really think of PKU testing as predictive testing. I think we think of it as diagnostic testing.

DR. CHARACHE: Just two thoughts. One is just a practical one. When you appropriately say what information should be reviewed and point out that it can be literature information, not that generated by each individual unit with a test, particularly the home brews, what the laboratory that wants to offer the test does have to prove is that their test works like the literature and not simply that there is the ability to do that.

The other comment, which had to do with the labeling, I think it would be very helpful if we also request that the label specify what information must be included in the report form.

DR. MC CABE: I think we have had a good discussion. Just before we continue, because we are going to wrap this up fairly quickly, I would just like to say that I think this is an outstanding beginning from the Data Team. I would recommend, and part of what I

wanted to do was have some other discussion to see if anyone disagrees with this, but I would recommend that you try and finalize this with your team before the February meeting and come back with something at the February meeting that we could see as an entire Committee and consider at that time for approval.

It sounds like a key ingredient to that will be some definitions that you will need to work on, but I think you are nearly there from what I can see. I think this will give some time that we might be able to get some feedback from some other laboratorians and see what they think from some of the other industry representatives who I know are here and who Elliott might be able to help us make contact with to get feedback.

MR. HILLBACK: Ed, I would just like to add, I think it would be very important that we also ask for some feedback, maybe more feedback than we have been, from the clinician side of the house. If we are really talking about a collaborative effort to update data, we know where Muin and the CDC and the great job they have started to do and I think we can get to the laboratorians pretty quickly. They have been involved in this discussion for awhile, but I am not sure that the groups of clinicians have been as involved in maybe what our expectations are about how we update the status of clinical practice.

I think it would be interesting to get their comments on this approach as well in this interim period.

DR. MC CABE: Yes, unfortunately, Reed is going to join us late today. But he has been doing some of that outreach to the clinicians.

DR. BURKE: Yes, I did want to comment on that, in other words, that we already have feelers out in a bunch of different directions. I know, for example, also that Penny Manasco has distributed the draft for comment as well and we don't have comments back from all the companies that she has contacted.

So, I think it will be good for us to have additional time. What I think we can work on in addition to definitions in our interaction with professional organizations is at least

perhaps provide some more description and, therefore, some more clarity about what the steps are likely to be in the development of that second phase of clinical practice standards development.

DR. BOUGHMAN: In partial response to your last question, Dr. McCabe, in the FDA process there is the possibility that there can be requests for post-market data collection. That routinely is merely submitted to the FDA and then not necessarily incorporated in a revision of the materials that are related to that. However, as this Committee moves forward, Steve may be able to, in fact, work that in as an adaptation of a process in this pre- to post-market reviewing and standards process.

I would like to not only commend this group but give not so much a challenge but a supportive statement that says, in coming up with these definitions, I don't think anybody expects you to have gained an absolute consensus but convergence to terminology that will lead to consistent use of these terms, whether it is absolutely right or not, I think would be a major step forward.

MS. DAVIDSON: Yes, I just wanted to mention just to kind of bring our attention to also the limitations of what we are describing, having just endorsed the importance of it. I am thinking just about the numbers of it. I guess I am talking about myself, but the numbers of people who read or don't read the labels of the medications that they are taking.

So, I think that to think of this as a body of knowledge and data that is going to be evolving or developing and being integrated is important and it will reach some people, but it is important also to be aware of the limitations and think further down the line about some other mediums to be sure that real people are reached by the information.

MS. YOST: That is a really important point. Actually HCFA's been working on this as we speak because we have started to collect data -- well, we have always known along, based on the survey findings of CLIA-certified laboratories that the most frequent problem we find in laboratories is they don't follow the manufacturers' instructions, which is the labeling. We

have some other pilot studies on other labs that verify that. We are initiating a process to work with manufacturers and the Health Industry Manufacturers Association and other organizations to get the word out in other mechanisms using web sites or self-instructive videos or other types of ways of getting information across that is in the manufacturers' labeling.

That kind of dovetails very nicely into your plan.

DR. MC CABE: Very good. Thank you very much. Do you consider that a realistic expectation for the next --

DR. BURKE: Yes, if I am understanding. Finalize the report, add the issue of definitions and gather more information from interested parties.

I will say the Data Team, obviously, would welcome help from anyone, any Committee member, anyone in this room in terms of identifying appropriate organizations that would like to review and give feedback.

DR. MC CABE: I think it might be also good for the interagency group that I know has been meeting to consider some of these issues that cross agency lines because we are talking about some new ways of looking at things when we are talking about the pre- and the post-market -- another several of you here -- and maybe you could make that a point for the agenda for one of your discussions as well.

DR. KHOURY: Actually, Steve is not here, but I can speak maybe on behalf of all of us -- Judy is here -- that the group that has been meeting and will be meeting again is going to adapt or adopt the SACGT recommendations for the sort of continuum of pre- to post-market review and data collection. I think this is a great step in the right direction.

DR. MC CABE: Thank you very much.

Let's take a break. We will reconvene at 10:30. Members of the Committee, there is some coffee in Conference Room 9, tea, other things. There is a cafeteria on the first floor.

[Brief recess.]

DR. MC CABE: We will now turn to Mary Davidson for a progress report and discussion on the Rare Disease Testing Team's issues and I see it is the Rare Disease Low Volume Working Team.

So, Mary, if you could proceed and then we will follow that with a discussion.

Report from the SACGT Rare Disease Testing Team

MS. DAVIDSON: Good morning.

First of all, I just want to give us some background as to why we established this working team. If we all remember back at our August meeting, we ended up with a model, with two scrutiny levels, 1 and 2, and the primary criteria that were classified that would determine whether a genetic test that was up for review went into Scrutiny Level 1 or 2. The primary criteria that we came up with at that time was low volume and the other concern that was expressed I think, right at the end of that meeting, was the issue of rare disease testing and we wanted to be sure that there was some committee at the issues of the rare disease tests and the rare disease community to be sure that whatever review process we set up really serves their interest.

So, we came up with this kind of hybrid two-headed committee, low volume rare disease testing.

Committee members, I am the chair and the members include Kate Beardsley, Pat Charache, Steve Gutman from the FDA, Alan Guttmacher from NHGRI, Michael Watson, Virginia Wanamaker from the Division of Laboratories and Acute Care at HCFA, Roberta Pagon from Gene Testing Clinics, Janine Lewis who is a genetic counselor at the Genetic Alliance, Vicky Wittemore, who is also at the Genetic Alliance and Henrietta Hyatt-Knorr, who is the director of the Office of Rare Diseases.

There were three tasks that were initially identified for us to complete before this meeting. The first one was to really gather information from laboratory experts and also from the

rare genetic disease testing groups, just to try to get some sense of experience and the track record that these groups have experience with genetic testing already in use.

Secondly, our task was to define low volume tests and to think about what low volume really meant in an operational sense. That I would say turned out to be the most difficult and interesting of our tasks.

The third task was to develop some criteria that might raise the level of review for tests of low volume assigned Scrutiny Level 1, that might raise a test that warranted it back to Scrutiny Level 2.

So, moving ahead, we began thinking about volume as a primary filter and some of the considerations that we really had was looking at this as a public health model. In other words, really trying to help the FDA then focus review efforts and resources on tests that would affect the greatest number of people and potentially risk the greatest level of harm otherwise.

This would be such as population-based testing, newborn screening. Another one of our motives was just simple pragmatics, wanting to be sure that a classification system and looking at low volume and in defining that term, that we ended up with a number of tests in Scrutiny Level 2 that was really doable, recognizing that Scrutiny Level 2 would be a much more time consuming and detailed in terms of data analysis process.

Again, our third consideration was the impact on rare disorders because, again, we felt the rare disease community needs special consideration as we go through and develop this model. Finally, we wanted to be sure to reduce the burden and cost to smaller laboratories, laboratories particularly in academic settings that might be providing a small number of genetic tests per year, for whom the more rigorous Scrutiny Level 2 procedures might really be prohibitive.

So, as we got into our discussions, I think probably to little surprise to many people in this room because I think low volume has been an issue that has been discussed in several of our teams, as well as several groups that have met outside of our team. We began to

have some concerns, as well as some interest, just in the complexity of using volume as a first cutoff criteria.

I think one of the first things that we realized was that low volume really does not equate with genetic testing for rare diseases. This became really obvious to us from the Genetic Alliance as soon as we sat down back in our office and began walking through several rare diseases through the model. The rare disease tests really have many purposes and uses. Some are population-based and high volume; take, for example, PKU and newborn screening. Some have low volume, but we felt registered high on a social risk scale tests such as predictive testing for Huntington's disease.

So, what we kept coming back to was that test volume is really a kind of illusive and I guess what we always knew was an arbitrary number. The third consideration we had was that we wanted to look very carefully at the definition of volume and be sure that we were talking from the very beginning about projected future volume, rather than initial volume since -- this is kind of picking up on some of Pat Charache's concerns. We wanted to be sure the new tests that started with a low volume but ultimately were designed for population screening would receive the level of review that they warranted because of their ultimate use in broad numbers of people.

We kept coming back to the issue and the criteria of usage and social risk as being perhaps a more relevant determining criteria than volume. In every case we had flow charts, and we will get to them in a minute, where volumes, low volume and high volume, while they were the first criteria, there were options lower down in the flow chart for kicking tests back into Scrutiny Level 1 or from Scrutiny Level 1 to 2, based on usage and social risk.

It seemed to us that we need to take another look at the model that we set up in terms of putting volume as the first cutoff criteria.

Our first task was information gathering and I have already given you some of the areas, some of the places that the team has really arrived at, but let me go back and tell you that what we did in terms of information gathering is that we went in particular to the Genetic

Alliance has a rare disease list serv of over a hundred rare disease groups. So, we went to them with a series of kind of quick and dirty questions, just to begin to get their interest and begin to get the feedback from those groups about what their experience has been, again, very much from the consumer and family perspective of what their experience has been with genetic testing so far.

I will come back to that at the end with just some anecdotal summaries of what those groups have said. This is an area that we wanted after this meeting, really building on the discussions today to go ahead and develop another questionnaire that we will be sending to these groups and following up on to get more information.

Secondly, and I have already mentioned this, I will just go over it briefly, is that we just kept circling back to concerns about test usage and social risk. In particular, let me just pick out one that I think this community really hasn't looked at, but the team began to really discuss, and that is, that in terms of diagnostic testing, I think that we had included prenatal testing under diagnostic testing and it became really obvious with team discussions and discussions with the rare disease community that we need to consider breaking out those two test categories and looking at diagnostic testing and someone who has had clinical symptoms as being in a different category in terms of determination of Scrutiny Level 1 or 2, then a prenatal test, which would be a diagnosis based on the results of the genetic test itself.

Again, we kept looking at the progression of tests from diagnostic prenatal and we spent some time, thanks to Steve Gutman from the FDA, thinking about human device exemptions and we were considering HDE, which is the short version of human device exemption as a way to provide a less burdensome review process for some very, very low volume rare disease tests that would perhaps not benefit from classification, even at Scrutiny Level 1 or 2. I wanted to bring this information to the Committee for consideration.

This is not on the level of a recommendation, but we did take the time to think about using HDE as a kind of precedent in the case of very, very rare diseases. Let me just give

you some of the background on HDE in case you are not familiar with it. HDE, the Humanitarian Device Exemption of Safe Medical Devices Act of 1990, applies to diseases and conditions that affect fewer than 4,000 in the United States. That translates into an incidence number of 1 in 62,500 persons.

Then further, according to the HDE information posted on the web site and our understanding of that information, devices -- and I hope that Steve is still here? He is not here.

DR. MC CABE: He had to step out. He is on a conference call.

MS. DAVIDSON: The devices may qualify only as long as the number of patients treated or diagnosed with the disease is less than 4,000 per year, but the incidence has to be fewer than 4,000 persons in the United States. So, when we began looking at this in terms of the rare disease population, we felt that this was really going to affect very, very few of the rare disease groups that we are in contact with.

There still may be a place for consideration of the HDE as a precedent for a third scrutiny level so that tests that are really only a handful per year go through a different process, but we didn't feel that it really answered the question of whether rare diseases need some special considerations.

Options. We can stay with the original model and I think -- Susanne, do we have those flow charts? Yes. So, we can put them up then afterwards. We can stay with the original model that uses low test volume. We still have to come up with a number for that, but what this committee is proposing is that there are certain limitations, particularly based on what we feel are the importance of looking at social risk and other factors in assigning a test to a scrutiny level.

We could also consider using HDE as a surrogate for some very rare low volume tests and develop criteria to determine the appropriateness of HDE or SL1 or SL2 review for a particularly low volume test.

A third option would be and I think this really picks up on discussions that already began in the last presentation and I know we are going to come up with Muin's

presentation after lunch but we could begin thinking about social risk perhaps as a first consideration on the flow chart as a first cutoff criteria and by social risks, I mean, we are talking -- I think this is no surprise to anyone but it would include population-based testing, predictive, presymptomatic, prenatal testing, testing for mental illness behavior, behaviors in tests for which there are no treatments and so on.

Finally, I just want to give you some brief feedback on the rare disease communities. This is the response of about 20 groups to our questions that we put out. I think it is no surprise, the four major elements that people identified were -- the first factor that everyone focused on was access.

It was just resounding among our groups that the review of genetic tests not inhibit access to genetic tests by individuals with genetic conditions in their families. People looked particularly with concern at whether the process might be excessively slow or onerous, that there might be a requirement of excessive amounts of data prior to preliminary review and release of the test for usage.

There was also concern about excessive burden on the place on the test developer to prepare for the reviews, such that the incentives might collapse and the test not be brought to review or to market.

Secondly, there was a lot of concern about cultural competence and I just want to bring our attention to the needs for cultural, specific data that has been collected during the development of the test that we need to think about how that can be handled sensitively and confidentially so that no one person or group or community is harmed.

Affordability, the review of genetic tests for rare diseases, it was felt, of course, that it should not result in any significant added cost for the price of the tests in or to cover review costs because that would really make the tests unaffordable to most individuals and the rare disease is already pressed by other medical and other financial pressures.

Finally, accuracy. There needs to be a compromise reached so that we will really maximize safety, quality and access to the tests, while minimizing risks. I think what we heard was that it is only human nature to really want it all, but the rare disease communities understand that there has to be a delicate balance that we are going to have to always be striving to maintain between cost review, access, and quality.

Susanne, do we have the flow charts?

I think maybe for the discussion it might be useful to put the flow charts up on the overhead. Thank you.

DR. MC CABE: Thank you, Mary.

Comments from the other members of the working group about the deliberations?

Discussion

DR. CHARACHE: Just one brief one. There was the meeting that Dr. Gutman referred to, which I was privileged to attend, in which there was a discussion about the humanitarian device exemption. It turned out that there is some flexibility in establishing that, but there was also a discussion of other members there that if the cutoff, which is now established -- I think it is a legal establishment at 4,000 per year, that almost none of the tests that we are concerned about exceed 4,000 tests a year. I mean, it is a very high percentage of those tests that small labs do are well under that and therefore wouldn't go for that anyway.

I think we were very struck by the need for the balance between being sure that the tests are accurate and being sure that access is retained.

DR. MC CABE: Joann, do you have any comments, since Dr. Gutman isn't here, from your FDA hat that you wear?

DR. BOUGHMAN: My only comment at this point is the experience that I have had in actually participation in FDA review when a device or a kit gets to the committee level

and that, in fact -- and Pat may be able to comment on this process as well -- that, in fact, there are, if you will, softer issues, not just numbers and issues of data.

There are matters of interpretation that, in fact, are discussed and taken very seriously so that at least at that level when you have the panel review and comments and, given that those panels include consumer representatives and so on, that I can only say that it would not be a stretch for me to imagine that some of these social risk issues could come into those discussions in a fairly routine kind of way. How we interpret or come down on those issues might be another point.

Pat, would you have the same feeling about the process?

DR. CHARACHE: Actually, I would have a lot of concern about it. I think it would have to be hard wired into one of the things that was being considered. I think this for two reasons; first, because the FDA has made it very clear in all discussions that they have never considered social issues and they don't know that they have the appropriate panel or people within the FDA to really address that.

Secondly, because one of the strategies underway to answer the large number of tests that are going to be put on their plate has been to think of non-panel approaches to review of these tests. So, I think it would have to be a requirement that these be considered and it would have to be worded in a way that was feasible to do.

DR. BOUGHMAN: The FDA process, the panels, in fact, not only are convened to evaluate individual tests, but I have been on panels in the past that, in fact, have been convened to develop guidelines for physician papers, white papers of a variety of sorts. In fact, in deliberations of this group you might make sure that the FDA answers questions about would it be possible to convene the right kind of group to, in fact, establish guidelines or discuss guidelines then that could be incorporated in the process.

DR. MC CABE: Further discussion of this?

DR. KHOURY: The only thing I want to mention at this stage because you will hear from me and Joe Boone this afternoon is the amazing similarities in the outcomes of the deliberations that this group came up with and there was no one from our group involved with the rare disease discussion, but both at CDC, as well as with the Lab Forum, different groups reached exactly the same conclusions.

I would like to put some alternatives on the table, if you guys wanted to do it now or later on as part of our discussions. There are some potential solutions to what looks like a quagmire right now.

DR. MC CABE: Well, if you could briefly put some things on the table because I think this has been a concern. The volume was a public health -- that was why it was put on the table originally, that you deal with those that have the greatest impact.

What we have found is that it is difficult to assess what volume is. So, if you could help us, that would be --

DR. KHOURY: I will definitely try to. I think that test volume -- I mean, if I want to paraphrase everybody's conclusions, it is sort of an unattainable goal, but there are other ways to get at the public health impact by reversing some of these boxes. I have my own flow diagram I can show you, by relying first on the population use criterion, second on the rarity or commonality of the disease. So, things, for example, like newborn screening, where the test volume is high, but the disease is rare, like leukemia and others, they will be shifted immediately at the top because they are best for public health consumption, essentially where the whole population is tested.

DR. MC CABE: Shifted which way, Muin? To a higher scrutiny level?

DR. KHOURY: Right. And anything that deals with population use, which is now, I can't see very well, but the population-based box is on the second step or third step and will put it further up and then the second criterion would be the rarity or, I mean, the prevalence of the disease itself.

Well, we can briefly do this now.

DR. MC CABE: Yes, if we can do it very briefly because I want to have some further discussion.

I think the thing that we should recall, though, also in our recommendations was the tests that are currently in position with -- have a different review so that the newborn screening test for which there is considerable experience would have a very different review. It would only be new newborn screening tests that would undergo this kind of review.

DR. KHOURY: So, if you take a few parts from here on -- actually, you all have this in your packet. There is a CDC parcel --

DR. MC CABE: It is in the green packet.

DR. KHOURY: If you start by intended use being population-based or targeted, sort of, again, new tests, anything that is for public health consumption will be shifted to the level two at the outset. If the answer is "no," then you go down to the question of whether the disease is common or rare. If there answer is there, and we can play around the cutoff of 1 in 10,000 or 1 in 20,000 or 1 in 60,000 -- if the answer is there, then it goes to either Level 1 or humanitarian device exemption. But if the answer is common, then you ask the question of whether it is predictive or diagnostic.

So, basically according to this scheme, what goes into Level 2 are things that are going to be used for population use or those that are going to be predictive tests for common diseases. I think I will leave it at this point because we have a lot to chew on.

DR. BURKE: I am not going to comment directly on the change in order of population screening and volume and the replacement of volume with prevalence, though I think that does represent a solution to a problem that several groups discovered, which is there isn't a good way to measure test volume. I want to talk about something further down the screening pathway and that is the issue of diagnostic versus predictive. I already mentioned this earlier.

I want to speak directly to Mary's comment about prenatal testing and that is at one level, I think we can say prenatal testing is a diagnostic test; that is to say, it is intended as a diagnostic test. The usual standard of practice is to require an extremely high level of predictive value before a test would be used for prenatal testing and, obviously, serious decisions are made on the basis of prenatal testing with the assumption that there is a very high predictive value.

So, the question I would have and I think it is part of our discussion about what is a diagnostic test really has to do with are we trying to accomplish in Scrutiny Level 1 and Scrutiny Level 2 and how would that inform us about whether a prenatal should be viewed as predictive versus diagnostic.

From my point of view, I think it is reasonable to call it a diagnostic test. The level of scrutiny at one -- I am talking about pre-market review now. The pre-market review issue is a pretty straightforward issue. It is what kind of evidence is there that this test has the predictive value that we would normally expect for a prenatal diagnostic test.

If we take that approach, we might consider putting prenatal tests in Scrutiny Level 1, but if we did so, we would be, I think, saying two things. One is that Scrutiny Level 1 involves different kinds of scrutiny for different kinds of tests because the predictive value we would require of a prenatal diagnostic test is higher than the predictive value we would require of a diagnostic test for a symptomatic person. I think that is one point.

I think the other point is that there are, as Mary outlined, a lot of social issues that come up with the use of a prenatal test. I am not sure those social issues, the ones that are raised by prenatal testing, are the ones that are incorporated into our review.

I think with a pre-market review, I think with prenatal diagnostic testing, the issue really is accuracy and then whether you would use the test, how you would use the test, and in what counseling settings you would use the test are not so much a matter of FDA or CLIA review as they are a matter of accepted practice standards.

The other thing I would ask people to be thinking about because we are going to wrap this up around 11:15, we will have some time for broader discussion this afternoon, that -- I also want to make sure that before we leave the working groups' comments that we really focus and any of the public who might have comments about these issues, there will be time for public comment this afternoon. So I would urge you to please let Sarah or one of her staff to know.

DR. LEWIS: I agree with Mary and I think you did a really nice job of delineating the dilemma between access and accuracy. I would just like to point out that access to a test that hasn't been proven accurate or valid is not necessarily good access. So, I worry a lot about using numbers alone as a criterion because it seems to me when I do research, the smaller the sample, the stricter become the criteria for proving significance.

To have access to a test that gives garbage as information may not be in the service of anyone.

MS. HUDSON: Muin, I have a question about your revised flow chart and specifically it looks like all predictive tests, unless they were rare, would fall into Scrutiny 2 because we have eliminated or you have eliminated this last category of effective intervention and social risks that allow some predictive tests in the old paradigm to be moved into Scrutiny Level 1.

I think that was a comfort to many of us that they would be a way of having predictive tests in a low barrier review framework.

DR. KHOURY: Can I answer you now or in the afternoon?

DR. MC CABE: I would rather not get into an extensive discussion of your model. I saw your comments more saying there might be some surrogates for volume. We can get into the model this afternoon, if that is okay.

DR. CHARACHE: Like Wylie, my concern is to this differentiation between diagnostic and predictive as determining whether it goes from 1 to 2. I do have a proposed

solution. But I will tell you that when eight different, very disparate genetic entities were given to the Genetic Forum to see how it would work if you use that as a descriptor, all four groups looking at the eight tests concluded that there would be no such thing as a Level 2 test because every

test --

DR. MC CABE: As a Level 1 test --

DR. CHARACHE: As a Level 2 test because everything would be -- the review per the FDA is only what the manufacturer says is intended for that test. So, every manufacturer is going to say it is for diagnosis, which would automatically put it into Level 1.

So, this is a reality that is also true and this is one of the two key points that CLIA focused on immediately. The problem that we would only have Level 1 tests.

Now, one of the things I would like to suggest for Wylie's group is that now is the time to see what the difference would be in the review from Level 1 versus Level 2, so we can see and get a better feel for what things would go into it. Level 1 probably would require everything that Level 2 did, but perhaps in a different degree. I think this would be very helpful for the group to help sort out. We were very concerned about using diagnostic versus the predictive as a discriminator for putting things into Level 1.

DR. MC CABE: Muin, did you have a comment?

DR. KHOURY: Well, again, I'll say more extensively in the afternoon, but it boils down to intended use and off-label use. There is so much you can do to regulate that, but if it is part of the insert on the package that this test is for diagnostic -- people who are sick and then -- I mean, there is no way really around it. You can regulate things to death, but I just wanted to say something in response to Wylie briefly.

One way to think about diagnostic versus the rest of the world is perhaps by throwing out the label predictive. Diagnostic is when you have a person who is sick, who has clinical signs or symptoms at the time of the testing. That person is a person who exists.

Anything else, including a fetus or a presymptomatic person, let's say with Huntington's or OKU who you know are going to get sick, I would put in the other category for a simply reason, because of the penetrance and expressivity of most genetic diseases. I think we can probably say for sure, the magnitude of -- for most of these diseases, even if you think they are going to get it, they may or may not get it. So, my simple mind says if you are sick at the time of testing, that is diagnostic. Anything else should be put in that other box. But that is obviously a point for discussion.

DR. MC CABE: Wylie, do you want to respond?

DR. BURKE: Yes, I want to respond to that by saying I think that has the virtue of being a simple definition, but -- and actually I think I went into this diagnostic versus predictive thinking that was the right way to go and now I feel very uncertain about that being the right way to go.

I will give you a few examples. I have already mentioned PKU testing. PKU testing is done on an asymptomatic individual and yet it is functionally diagnostic. That is how we use it.

Let me give you a few other examples, just to lay out the ground work. I think it is different to do a prenatal test for let's say Down's or Tay-Sachs disease, where we have a very high degree of certainty that we are identifying someone who will be affected in the future, than it is to do a BRCA-1, 2 test in which we are predicting a probability of breast cancer. I have trouble combining those into the same category.

I think it is also fair to say, as I already indicated earlier, prenatal tests have unique issues, probably carrier tests have unique issues. It might well be that we need to think in terms of a protocol of scrutiny that is related to the purpose of the test.

But, to me, that sort of -- the category that I think we were really worried about in Scrutiny Level 2 is all those issues that come up with BRCA-1, 2 testing and APO-E4 testing for predicting Alzheimer's. I mean, I think I would use those as models for the kinds of issues

that we are concerned about and to use yet another example, I think those are very, very different from using a highly predictive test for a von Hippel-Lindau mutation in the setting of a family where von Hippel-Lindau disease is known to occur.

DR. MC CABE: One of the things that this brings up and might be good for you to, as you are working on developing and finalizing your data for the February meeting, also think of some examples and run some models with specific examples for us.

MR. HILLBACK: I guess, Wylie, I was reacting to your comment about all prenatal tests either being considered diagnostic or predictive. Historically, which is the precedent you cite, we may be in that mode, but I think that the regulatory scheme we want to talk about is one that is going to work for the next ten years. I get very nervous in sort of making those bright lines that clearly.

Then I heard you come back and say in response to Muin that you wouldn't for other kinds of tests be so limiting in the way you define the categories. So, I would rather not say every prenatal test is either diagnostic or predictive. I would rather look at what we know and how it is going to be used and allow our knowledge base to help us decide which side to put it in.

DR. BURKE: Just a brief response. I just want to note prenatal tests, I think, are in a very special category, at least in terms of current practice, because current practice suggests that, I think both on the consumer side and on the health provider side, that it is really not very acceptable to use the tests for prenatal unless the predictive value is extremely high.

MR. HILLBACK: But I also think you are assuming that there are only certain kinds of actions that one can take based on that knowledge and I guess there are other opportunities in the future where prenatal therapies are going to be not necessarily impossible.

Therefore, I would hate to create a rule that says, hey, anything prenatal is predictive when it might really be diagnostic and usable and useful clinically. So, I hate to make a rigid line today.

DR. BURKE: That is a fair point. We might be able to say prenatal in the absence of therapy. But I take your point.

DR. MC CABE: Victor. And then after Victor, then we are going to wrap this up, but I will ask Mary to think about what would be your focus for between now and the February meeting.

DR. PENCHASZADEH: I just wanted to direct this question of the prenatal testing because this illustrates the fact that almost any category that we will end up using will be arbitrary because, in a sense, of course, when you do a prenatal diagnosis, you are doing diagnostic testing, but on the other hand, you don't know the phenotype of that fetus. From that point of view, you are making an inference based only on a lab test.

So, in my view and essentially because of this and because of all the social implications of prenatal diagnosis and without getting into a discussion of whether it is diagnostic or predictive, I think that it should always be of a high scrutiny level.

You mentioned one of the examples of Down's syndrome and Tay Sach's, but really makes us comfortable using those tests is essentially the 20 or 30 years of experience that we have already. If we are talking about new tests and not only for the susceptibility, predisposition testing, but also for deterministic genes, for which there will be new testing appearing and any test that appears in the market is technically feasible to do a prenatal diagnosis.

I think that again I would go back to the question of intended use and I am really concerned about the comments that Pat Charache made regarding all the loopholes that one will be creating by this categorization and allowing manufacturers to state one purpose and then get the test on the market and then use it for -- or allowing it or creating the conditions for its use for any other purpose.

I still think and just to boil down a prenatal diagnosis, it is a separate category that should require a test for high scrutiny, if at least only for social reasons.

DR. MC CABE: Thank you.

Mary, what would you recommend that we have your group focus on between now and February?

MS. DAVIDSON: I think certainly following up on the interest that the prenatal issue has raised in this group, I think that that is an area that this committee can begin looking at.

I wanted to go back just to let you know that one of the ways that we really arrived looking at prenatal issues was that in our questions to the rare disease list serv and in asking them in their experience what the utilization, what the usage or the intention of the genetic test was at it progressed, the prenatal usage was right at the top of the list. They saw that as being a primary use of the test once it comes on the market.

So, I think that it makes sense for us to look at those issues, both from the rare disease community, but also to get some idea about numbers.

The others that we were planning to gather additional input from the rare disease groups, as well as from laboratories to get some better sense about how Level 1 scrutiny and Level 2 scrutiny, how that would affect access. Of course, that would be in coordination with the Access Working Group.

Otherwise, I think that after we have our discussion particularly this afternoon with Muin's presentation, that we may want this team to come back and revisit what our primary issues are. I am very interested to understand the issue of prevalence since the name of our team is "Low Volume Rare Disease Tests."

DR. MC CABE: The other thing that I might suggest, again, and with respect to the rare disease testing, is to perhaps talk to Judy Yost about some of the issues there in terms of back to our recommendations about providing technical assistance to the research laboratories to try and improve the penetration of CLIA approval among those because I think that is also very important for this. So, perhaps you could include Judy in some of those discussions as well.

MS. DAVIDSON: Great.

DR. MC CABE: Because that was in one of our recommendations in our document and it would be good if we worked on we were actually going to implement that.

Thank you.

We are now going to move on to Dr. Judy Lewis for a progress report and followed by a discussion from the Access Working Group and some of the outreach efforts that have been going on.

While Judy is doing that, I'll just comment that our computer operator at the last presentation was Sharon Terry and there was an article in Nature, October 19th, featuring Sharon and her son about PXE International and their approach to having the patients and their families involved in an ongoing way in patents and research. I don't know -- do we have a copy of that in our packet?

But I congratulate you for your efforts and the visibility that you are getting for this.

Judy. Thank you.

Report on the SACGT Outreach Effort and the Access Working Group

DR. LEWIS: Thank you, Ed.

I want to report on the work of two separate sets of efforts that are together but compatible and that is the Access Working Group and also to give people an update on our outreach efforts.

First of all, the working group, who has been working on access, consists of myself, Ann Boldt, Pat Charache, Mary Davidson, Victor Penchaszadeh, Reed Tuckson, Michele Puryear from HRSA, Teresa Clark from HCFA, David Witt from Kaiser Permanente, and Cecil Bykerk from Mutual of Omaha.

David is a medical geneticist at the Regional Genetics Program at Kaiser Permanente. Cecil Bykerk, for those of you who don't know him, is an executive vice president

and the chief actuary of Mutual of Omaha and Teresa Clarke represented HCFA on Medicare and Medicaid issues.

We have had one conference call and during our conference call we had a preliminary discussion of some of the reimbursement practices by managed care organizations, indemnity insurers, Medicare, and Medicaid. The major outcome of our conference call was that we planned the session that will happen tomorrow morning on reimbursement. We discussed some of the topics that the work group would like to see the speakers address and a list of questions that were developed as a result of this conference call can be found under Tab 9 of your briefing book.

Tomorrow, after the presentations, we are planning to have a working lunch for our Access Group so that we can, after we have a sense of what our presenters say and what kind of public comments we hear, we can then plan our next steps.

Just to give people a background for the presentation tomorrow morning, the purpose of that presentation is to provide all of us with information on current practices and policies for the reimbursement of genetic tests by various types of public and private health industries, including for-profit, not-for-profit, managed care, indemnity, preferred provider organizations, point-of-service, Medicare, and Medicaid.

The goal of the session tomorrow morning is to enhance our knowledge of reimbursement issues to provide a foundation for the Committee's exploration of access and reimbursement issues related to genetic test services. The public comment period scheduled after the presentations will give us an opportunity to hear other perspectives about reimbursement issues.

The presenters that you will hear tomorrow morning, include Jacquelyn Sheridan, who will be talking about Medicare and Medicaid; Dr. David Witt, who will be talking about the not-for-profit managed care sector; Dr. Victor Villagra, who is an internist and chair of the Technology Assessment Council for CIGNA, to talk about the for-profit managed care

sector; Cecil Bykerk, to talk about the for-profit indemnity insurance sector; and Allan Bombard, who is the medical director for women's health for the Pacific and Western Regions of Aetna US Healthcare to talk about for-profit managed care, preferred provider organizations, point-of-service, and indemnity insurance.

In another area, as requested at the August meeting, the Genome Research Institute has provided us with a written overview of ELSI activities and research projects in the areas of intellectual property. The analysis points out that the NHGRI's legislative authority includes specific reference to the role of intellectual properties in the ELSI research agenda. It refers to -- and I quote -- "reviewing and funding proposals to address the ethical and legal issues associated with the Genome Project.

This includes legal issues regarding patents. The background and grant descriptions were included in your briefing book under Tab 5.

The ELSI studies include and analysis of the impact of gene sequencing and patenting on the further development of technology, which resulted in the development of the theory of the anti-commons. This is the work of Rebecca Eisenberg. David Blumenthal's work includes an examination of academic industry relationships in genetics and data sharing in genetic research.

Also, Mildred Cho's research right now includes case studies to examine the effects of gene patenting on research and development and on the integration of genetic tests into clinical practice. Now, during the public consultation on oversight of genetic tests, concerns were raised about access to and cost and quality of genetic tests. In response to these concerns, SACGT held a session on human gene patenting and licensing practices and access to genetic tests at our June 2000 meeting.

The panel was composed of experts in the government, industry, academia, law and clinical, ethical and legal communities to provide us with an understanding of how patents

and licenses work and how they enhance the public good and what concerns are being raised about them.

In response to these concerns, a letter to the Secretary has been drafted for Committee review and discussion. The draft of the letter is under Tab 5 in your briefing books. SACGT agreed that it is not the appropriate body to explore patent and licensing issues in-depth, but we believe that there may be a need for further study by appropriate experts.

For example, a comment that is taken from the draft of the letter that I am hoping we will discuss shortly, and this is a quote, is "While we wish to see the development of genetic tests and gene-related technologies continue at its present pace, we would also like to ensure that these tests are of high quality and both accessible and affordable to the public.

In terms of future activities of our working group, these are the areas in which we would think it would be appropriate for us to focus after this meeting. In the issue of health care disparities, one of the questions that we would like to see discussed is what is the appropriate focus for SACGT in this area. In terms of low volume and rare diseases, we need to coordinate the work we are doing with the team that Mary just reported on.

Now I would like to report on our outreach efforts because that was something else I was tasked to do after our last meeting. A letter was sent at the beginning of September to 13 individuals, who assisted the SACGT in the planning of our outreach process on the oversight of genetic tests when we requested their assistance in identifying the major questions and concerns related to the five areas that we chose to address.

We have received one response so far and you have got Dr. Lin-Fu's letter in your briefing book under Tab 5. One of the questions that we have for the Committee as a whole is whether and how we need to expand our outreach efforts.

In summary, some of the topics that I see as important for our discussion in the next few minutes are to look at the patent letter and to reach some kind of consensus on the next steps, which we should be doing with this patent letter. In terms of expanding our outreach

efforts, does the Committee as a whole want to expand our outreach efforts and, if so, from whom else do we wish to hear?

In the area of health care disparities, what is the appropriate role for the SACGT? Then I believe we need to work further to define access issues.

DR. MC CABE: Maybe you could leave those bullets up there, Judy. I think that might help with the discussion.

DR. LEWIS: Okay. I also have an overhead of the patent letter if we need that.

DR. MC CABE: Okay. We will need that, I am sure.

Discussion

Other comments from members of this working group before we open up the discussion?

[There was no response.]

Well, I am going to ask that we focus our discussion initially on that Bullet 1, the patent letter, because this is something that we have circulated as a draft to the Committee that there has been some feedback on. You will find in your green folder is a draft of the letter with the current feedback that we have received.

So, let's really focus the initial discussion on that.

MR. HILLBACK: Yes. I had several, I guess, questions on where we wanted to go with that. One was we focused the discussion -- and I wasn't sure where we ended it the last time. I thought our primary focus was getting more on the licensing side, given the feedback you got at the director's meeting at NIH and some of the other feedback addressing this to the patent side and trying to raise issues about fundamental patent policy was difficult.

That was one point. The other thing that bothered me a little bit about the letter and I think it is easily corrected and I apologize for not getting comments back but I have been on the road a lot the last week or so, is that I don't think the Canavan story was totally rounded

out in the letter in the sense that the concerns that were raised by the people that came here about the Canavan story stopped at a certain point in time and, in fact, market pressures, both from academic labs and commercial labs, as well as I think the patient organizations, did pretty dramatically change the way that particular patent holder did things.

So, the end result, after market pressures were given a little time to act, was if that had been licensed more broadly and the test is more broadly available. I am not sure the letter really reflects that at this point. So, I think there are two questions. One is -- or two major points -- one is I think this seemed to be a little more aimed at patents, rather than how patents are applied than I thought we were going to be and, two, I would just like to make some suggestions about how we make sure we portray the Canavan story in its entirety.

DR. MC CABE: Yes. I think that we were trying to address both the patenting and licensing. The way we used the Canavan disease vignette in -- let me just read it. It is a little bit hard to read off the screen there. But in the middle of paragraph 3, it says "Second, inventions can be commercialized in ways that adversely affect accessibility to and the cost and quality of a product, for example, initial restrictions."

So, we were focusing really on the initial issues there and the intent was not really to tell the whole story in a sentence or two. But, for example, initial restrictions in the licensing of the genetic test for Canavan disease limited the number of tests performed annually and affected efforts to offer broad karyoscreening to certain populations.

SACGT was also told that laboratory directors were being deterred from offering tests beneficial to patients by restrictive licenses. So, we were trying to deal with licensure there. The goal was not to tell the whole Canavan story, but to discuss the early deterrent that was caused by the licensure.

MR. HILLBACK: But I do think that leaves the impression that the government or some other body may need to step in when the fundamental principles that govern this now are market forces. In fact, market forces did prevail and to not close that leaves a call to action that

may not be as important a call to action. I think it is not something that I am comfortable with personally.

DR. LEWIS: Can I speak to that point?

DR. MC CABE: Okay. Judy, go ahead and then Wylie.

DR. LEWIS: I think part of the issue is market forces came to bear, but market forces were brought to bear because of the extraordinary effort and the fact that there may have been some harm to a particular patient disease group and part of, I think, our concern in writing this letter is we didn't want every patient group to have to go through that. Market forces did come to bear, but it was at somewhat of a cost to some of the humans who suffered from that particular condition, who didn't necessarily have the resources. So, part of the reason for telling this story is because we don't want this to have to be repeated with every particular patient group.

I think it is important to learn from history.

DR. BURKE: My comment follows very much upon that and refers specifically to the issue of licensing and patenting. I would favor keeping the phrases in the letter as they are, patenting and licensing. I completely agree with Elliott that I came away from our panel discussion last time thinking that the solutions to problems that exist may well lie in licensing changes rather than patenting changes. But I think the most important point we are making in the letter is that we are not the experts. Rather what we are saying is this is a domain that bears further study.

We are not the people who should do that study, but we just want to alert those who do, that issues of quality, accessibility, and cost are very important issues that could be affected by patenting and licensing. I think it is just very important for the letter otherwise to not imply conclusions about where the solutions lie, but rather leave those to the appropriate experts.

MR. HILLBACK: I guess it still -- it wasn't just the Canavan's patient organization that had an impact. The laboratories, both commercial labs and academic labs, were just as active to say this is not the right way to do things. We have in this country an orphan drug

law that creates monopolies and here we are sitting her saying we are not going to let a lab have a monopoly. We are asking the Secretary to start examining that and I think we need to tell the story in a full way so that it is clear what the whole story was and not leave it half told.

That is what concerned me about the way that that paragraph is written. I am happy to provide some of the language, which I don't think is to try to say that it wasn't ever a problem, but to make sure that the circle is closed so it is clear.

DR. MC CABE: Sarah has some language here that I will let her read.

MS. CARR: Well, maybe after the sentence about the Canavan disease problem, you could say, "In this instance market pressures and concerns from patient groups and laboratories..." -- and maybe "licensure" -- "ultimately made the licensure more broad," something like that.

MR. HILLBACK: I agree. I think that is what I was trying to get to is that not to say that there weren't issues raised and there is some language that I have done some of and some other folks in industry have helped work on that I have here, that basically says that. It says we are not trying to say it didn't happen. We are trying to say it was at least to a significant degree resolved and it still raises concerns and the language we have still says that. I just think it is not --

DR. MC CABE: A sentence like that or you have some language that maybe you could circulate to the group?

MR. HILLBACK: Yes, I can do that.

DR. MC CABE: Okay. If you could get that to Sarah so we can circulate it.

DR. BURKE: I think, though, in due respect to the point you are making, Elliott, that, in fact, I think the conversation we heard, the discussion we had in Committee said we are not sure whether market forces should be left to resolve or whether more investigation. I think this letter should basically say that. Here is an area of potential concern vis-a-vis quality, access, and cost of tests and we are not sure what the solution is and we don't have the expertise to

determine it. Maybe nothing needs to be changed, but maybe something does need to be changed.

I think we have to keep that. There shouldn't be an implication that in this instance there was a problem but it got solved.

MR. HILLBACK: I think we need to be careful. We are trying to now differentiate genetic testing from all the other medical products, all sorts of other things and I am not sure that we are going to get ourselves into an area that makes that --

DR. BURKE: But, again, we are not saying that. What we are saying is that there is a potential that patenting/licensing laws, as they now stand, may create problems for quality, access, and cost of genetic tests. We are not saying they do. We are just saying there is a possibility.

DR. MC CABE: There is a good bit of that in the next paragraph certainly after that.

DR. BOUGHMAN: This may seem minor, but in paragraph 2, where we say the panel provided SACGT with an understanding on how patents and licenses, I would prefer us to say “an appreciation for” or “some understanding of” that would emphasize further that we are just scratching the surface here.

MS. DAVIDSON: I wanted to pick up on, I think, basically Elliott's comments about using Canavan group as an example from a different perspective. Again, this is the rare disease community perspective. I think that Canavan has limitations as far as an example. In many ways, it is not a black-and-white issue.

Our understanding is that access -- that there have been no incidence of people not being able to attain a Canavan test. So, the other issue has come up in the rare disease community is that the cost of the Canavan test, while I can appreciate that to some people it seems high, relative to rare disease tests, it is extremely low.

I don't have -- and this is all anecdotal. So, I can't really give you much more than that. But it has been a feeling that Canavan, from the rare disease community's perspective, doesn't really well represent and doesn't really kind of argue the point.

The other piece in all this, what we have been hearing very clearly from groups, is that it is important to look at licensing and the benefits of licensing in both the restricted and unrestricted sense, that when you are looking at rare disease tests that may need profit incentives that come with restricted licensing, to be sure that that test is actually developed. So, I mean, we are hearing this loud and strong from quite a number of our groups that feel if something went through a patent and licensing process was license on an unrestricted basis. Then companies would kind of throw up their hands and say it is not worth my putting in all the time to develop it.

While it touches on it, I don't think that is as strong, as clear as --

DR. MC CABE: Is there language you would wish to insert?

MS. DAVIDSON: I could work on it.

DR. MC CABE: If you could work on that then.

DR. PENCHASZADEH: The only point I want to make is that probably we should emphasize and I think the letter does that, in the outcome, the type of outcome situation that we want and that is essentially practices that should not affect access, cost, and quality of tests. I am not sure about the relative role of market forces versus pressure from the patient community and the level of the directors in the Canavan disease.

So, I would not be in favor of identifying which one of those pressures had an impact in redressing the issue of Canavan disease. Now, listening now to Mary, I would -- probably Canavan disease was a peculiar not representative example of larger issues that have to do with patenting and licensing, but at this stage I am not sure whether we should keep the example simply B

DR. MC CABE: Well, it was an example that was presented to us. I think that is partly why it is here and we also know that examples are important in teaching principles. I would point out the cost issue, part of the reason why the cost was considered high, though, might be low for a diagnostic test, the community was really trying to develop this as a screening test and it was a significant percentage of the total screening test that was being developed.

So, that was part of -- it gets back to what is the use of the test because screening tests are typically less expensive than diagnostic tests.

DR. HUDSON: I think the concerns of the Committee are very well represented in the letter in the absence of the Canavan's example. I think we could, in fact, delete it so that we don't get hung up on interpretations of what was and was not the case. And because we do include a summary of the panel session as an attachment to this letter, I would expect that that is fairly well hashed out in that summary.

DR. MC CABE: Okay.

MS. BEARDSLEY: I will withdraw. I was going to say the same thing.

DR. MC CABE: Okay.

MR. HILLBACK: Yes. I think one of the other things that if we remember all of the various people that talked, I mean, we got into this issue of competitive issues in the lab industry and I don't think we want to get into does every lab have the right to be able to license every test.

As much as in our own business, Genzyme at one point in time was interested in licensing the BRCA 1 stuff for Myriad. I think Myriad presented -- and we have competed with them rather head to head on some things. I think they presented some good arguments why, given the complexity of that test, they didn't want to license it to everyone and their uncle and would do something in a much more controlled way.

I can't say I have always been personally a fan of this because we have competed head to head, but I think they made some good arguments. So, I don't think we want to get into

the point of are we creating a fairness for all that every lab has to get access to every test situation. I don't think that was the point. The point is access to the patients and can the patients get the right test done by the right lab in the right way.

I don't think we want to go too far to make this an industry issue versus a patient issue. Patients are where we were coming from, I believe.

DR. CHARACHE: Maybe we may want to consider strengthening the impact on quality. Specifically, there are two areas in which it is problematic. When there is more than one or two laboratories doing a test, you can't prove whether their test has gone off-line or not. There is no possibility of proficiency testing and using comparative laboratories to determine if they are getting the same answer they used to get. So, there are a lot of problems with documenting quality when you have a single laboratory licensed or a small group of laboratories licensed.

The second aspect of quality is that we see in our publications, scientists who do not put in the publication all the information that is necessary to get the right answer. I think hemochromatosis is an example. The primers were published but no the annealing temperature. We had a lot of good laboratories giving out bad data because they chose too high an annealing temperature.

DR. MC CABE: Thanks.

DR. BURKE: A comment on Elliott's comment and I hope, to me, a reassuring one and that is I think all the questions you are raising are very legitimate questions. I think some of them are captured in the fourth paragraph of the letter appropriately. I think it is extremely important that the letter have the tone that says maybe there are problems here and maybe there aren't and we are not the people to determine that, but we want to bring this to your attention because it may be appropriate for others who do have that expertise to determine it.

I think that is what you are saying and I completely agree that that should be the tone. I think that is the tone of the letter as it stands.

MR. HILLBACK: Yes, I don't totally disagree, but I would like to propose some wording over the rest of the day and I will get something --

DR. MC CABE: I am going to leave the letter now. We have had some suggestions. I would ask that you get those suggestions onto paper and to Sarah's staff. We already have two topics for the end of the day discussion today that may extend into tomorrow and that is the model and determining where we are going to go on that and then also the letter.

But let's move on to the other bullets, which have disappeared. Good. Thank you. Let's discuss the other bullets and help Judy and her committee with where to focus.

I am hoping, by the way, that we can come to some consensus on the specific language of this letter so that that can go out as a product of this meeting before the end of Friday. I think it is very close. I haven't heard any discussion to say let's tear it up and start all over again. So, it is just tweaking the language on it. We can work on that this afternoon, perhaps even on line.

DR. LEWIS: I think timing is an issue.

DR. MC CABE: Let's look at the other bullets and a combination of expanded outreach efforts, health care disparities, and further define the access issues.

I am going to pick Bullet 3, health care disparities. I think that others can talk to Judy and her colleagues about expanding the outreach efforts because I think it has been one of the principles of this group that we want to have broad outreach and we were challenged to do that at the very outset. So, I don't see anyone who – that is part of our charter. So, if you can help Judy with expanding that -- was it a more formal expansion of your group that you wanted, Judy?

DR. LEWIS: I don't know if it was for members of the group or just in terms of the kinds of efforts we should be making. When we had the consultation meeting in Baltimore, we promised people we would be back to them. We communicated with them by letter and told

them we will be back to them and I just think in terms of maybe as the other areas start to congeal, we will identify areas in which we could go.

DR. MC CABE: Good. So, if you can -- if people can work with Judy to help -- first of all, I agree, we ought to get back to people so to keep them informed of what our activities are but then always looking for new individuals that can be added.

The health care disparities, I think, is particularly important and part of this is from my own personal experiences. Having been one of the co-chairs of the Task Force on Newborn Screening, I was very impressed and continue to have a lot of activity with reporters about this. What they always bring up is the issue that you can have three tests in one state and 30 tests in another state and that is a health care disparity.

I think that Dr. David Satcher, our Surgeon General and Assistant Secretary of Health, has really increased the visibility of this concept during his tenure. So, again, I think the timing is right and I think that this is an area that has become part of the public consciousness. So, I would like to discuss the activities of this committee particularly in terms of health care disparity. So, if we could focus on that.

Do you want to lead off, Judy, with what you were looking for as guidance?

DR. LEWIS: In terms of access, I agree with you that I think it is important and I think newborn screening is one area, but I think in terms of access to genetic tests in general, that there are certain disparities. Part of our discussion tomorrow is going to deal with some of the disparities, I believe, in terms of reimbursement, but I think we might want to focus on other areas of health care disparity that people believe are appropriate for us to be looking for and we are just looking for some feedback from the Committee as a whole to make sure that there are areas that we are not overlooking.

DR. MC CABE: Yes, I am sorry. I was just using the newborn screening as an example of how high this has risen. I think that is underway. And Michele Puryear and her group, together with the Academy, the March of Dimes and others are moving ahead with that,

but it was more just the fact that this has become so much a part of the public consciousness that I think that we should definitely look for other areas where we can identify disparities in genetic health and try and see if there are appropriate ways of both bringing them some visibility, as well as dealing with them.

DR. LEWIS: Because it is clearly a priority if you look at Healthy People 2010. That is the goal.

DR. MC CABE: So, other areas then?

DR. PENCHASZADEH: I would like to call your attention to the only letter that we got back from Jane Lin-Fu and I think she points very rightly to a number of issues that I think are very kind of relevant in terms of disparities in access. That should not be restricted to issues of reimbursement and rare diseases, but the whole issue of minorities, issue of groups that are isolated linguistically and I would add, socioeconomic factors that may span across ethnicity and geographic differences. So, I think we should reemphasize our concern and address and study and make recommendations in terms of access to diminish disparities in genetic services and genetic testing stemming from ethnicity, socioeconomic status, linguistics and so on and so forth.

DR. MC CABE: I have been talking about this quite a bit because it is one of the things that has really been brought to my consciousness, thinking about how we are going to get information out to specific ethnic groups and the size of the ethnic groups becomes important. I know that some of the agencies are looking at developing databases that will begin to deal with this.

But if we are not able to deal with ethnicity and getting ethnic-specific mutation rates, we are not going to be able to counsel those individuals and they will be cut off from this technology. It has also brought to me the fact that some of these groups are going to be too small in the United States and I have heard others speaking about this also, but one of the things that

the Human Genome Project may be doing is bringing us together better for achieving some of these goals at an international level.

Because of small immigrant groups, we may not have the power within this country to address that. But, again, do they then become disenfranchised from this technology because of problems with sample size? So, there are serious issues that we need to grapple with that extend to the research, as well as to the service.

DR. KOENIG: I just want to reiterate. I affirm what Victor just said and also what you said, Ed. I think that the disparities issue is going to be of increasing importance and increasingly important in genetics because of the huge amount of research which is going to need to be done to tease out what really is at the bottom of disparities across different identified populations in the U.S.

I think one of the reasons we need to pay particular attention to it is because of our concern with tests that have potential social impacts. So, that gets into the whole arena of tests that might be targeted to particular subgroups and how that targeting is done and what language is used as we talk about targeting particular tests to specific populations. I think this applies both during the research phase of genetic testing, as well as to the eventual introduction of tests into practice.

DR. TUCKSON: I will reserve most of my comments for the subcommittee since I am on that, but I wanted to ask Muin a little bit, a quick question.

In addition to the concerns and the anxieties for harm, I am more interested, I think, also in the issues of opportunity and benefit. As we start to look at the relationship more between biological genetic profile and environment and the interactions that occur, is this something that it would seem that the Surgeon General really ought to put very much at the heart of the disparities agenda, so that we can begin to start to get very specific about being able to do the kind of counseling about risk and lowering risk and those kinds of things?

Is there a particular danger there or do you see a relevancy here to push that as a centerpiece of what we are doing?

DR. KHOURY: Are you asking me?

DR. TUCKSON: Yes, you specifically.

DR. KHOURY: Actually I want -- before you said what you said, Reed, I wanted to say the same words that in genetics that are these two sort of separate tracks. One is the premature or inappropriate utilization of genetic information, but the other part is the actual appropriate use when there is clinical utility, when you can reduce the burden of disease and disability or death, and then that technology doesn't get out to the people who need it.

I think those two issues can be approached a little bit differently from each other because one is an issue of access to health care. The other issue is more in the domain of the ethical, legal, and social implications discussions.

I want to agree with you, Reed. I think this is an agenda that is important to put forth and I think it transcends genetics in a big way. It is really not about genetics. It is about health and public health in this country and the point that I wanted to make earlier and I'm glad Wylie came back to it, was, as this Committee works on the issue of health care disparities, one of the things that it can do is recommend the kinds of research that need to be done, but also the kinds of data that need to be collected in the post-market phase to document the extent of disparities if there is any, document the extent of utilization of genetic tests.

This is something that perhaps Wylie's group can come up with. Let me give you a specific example. We can talk all we want about test inserts, about clinical utility. So, we say this test has clinical validity and clinical utility, but what is clinical utility in the real world. You know, is this population having access to the services? I mean, think about the simple example of penicillin prophylaxis for newborn screening for sickle cell disease. We know penicillin prevents septic death in kids with sickle cell disease, but are they actually having -- I

mean, we know in clinical trials it works, but in the real world, does it work -- how many kids don't have access to the simple information.

To me, that is all part of the post-market analysis that needs to be continued on an ongoing basis. So, the health care disparity issue is very much at the heart of public health and I agree with what you said Reed.

DR. LEWIS: So, what I am hearing Muin say is something about outcomes and looking at some of the outcomes so that we have some hard data.

DR. MC CABE: Reed and Wylie, brief follow-ups.

DR. TUCKSON: Very brief and we can get further down that road today. I am just glad to have it on the table.

Secondly is can anybody just help me to think a little bit -- when we talk about disparities, a lot of the times it is talking about -- in addition to culture, it is talking about race. I am wondering whether or not, if we continue to look at it the way it has been looked at, when the Genome Project goes forward and you start to know your genetic background, then the whole notion of your race starts to become different. I would just take myself, for example. I mean, I am not sure that I am going to quite understand all the different folk that are in me here. Something, obviously, has gone on here.

So, there is a bunch of people here. My sense of who I am once evaluated and, as you know, at Howard and others, they have advertised if you want to know what tribe you are from you can go and be evaluated. The question I am asking broader then is is there a need for a separate conversation before the end of this report about the notion and meaning of race in the context of the genetic era that would then help to inform the public discourse about categorization and disparities and the meaning of these terms for future health discussions.

So, I just sort of throw that weird ball on the table somewhere and you can think about it later, but I guess to just conclude what I am worried about is to have a discussion about disparities at the same time we are involved in a field that is going to redefine the nature of those

words or could and to not consider that may make whatever recommendations we do sort of obsolete by the very nature of the tasks we are involved in.

DR. MC CABE: Well, certainly what we are talking about is if we are going to have ethnicity-based counseling, then it is important for us to know which ethnic group we belong to. Is there going to be a misuse of that information also because we know it has been misused so it certainly is something reasonable to B

DR. TUCKSON: The question is what -- for many of us it would be what ethnicities groups do we belong to and secondly would be as to what does that mean in terms of health status.

The poor status of folks who are called black, who may have so many different kinds of permutations of stuff, it may not be that that is just a genetic issue. It is something else. This is a complicated conversation, which we may give some value to if we can figure out at least a way to start the public discourse.

DR. BURKE: My brief comment has to do with just agreeing with Muin that the Data Team should have a conversation that includes really how you gather data on clinical utility. I think that conversation has to include what kinds of data collection is mandated in some form or other as part of a regulatory process versus what kinds of data collection might be encouraged by laying questions out in certain ways because I would guess the former category is a relatively small number of data collection methods and the latter is really where we need to go.

I think how this connects to access is I would define the most crucial issue in access being the individuals having opportunity to access to services that can improve their health outcome. Put very simply if a genetic test can identify an individual who would benefit from a certain therapy, it is a real problem if eligible people don't get the test and don't get the therapy.

But to know that that therapy works, you need to have the clinical utility data that is often the hardest to get. So, I think that is where the issue of access connects very powerfully with data on clinical utility.

MS. BOLDT: As I have been listening to this conversation, too, I do see that we need to have a collaborative effort with the Education Working Group and that part of what I am hearing is that, even in light of some of Reed's comments he just made, that we do need to train more minority health professionals to be able to go out to get that access and to be able to communicate this type of information with individuals that still are identifying themselves with a certain ethnicity or race or minority.

DR. KOENIG: I can't let Reed's comments without following up to some extent and I think as we are trying to define or how we are going to define social consequences in terms of making recommendations to the FDA, we did have public testimony from -- I think one of the phrases that I remember from one of our hearings was someone saying what we need in the United States is a Manhattan Project about how we talk about race in terms some fundamental thinking about that.

I hadn't really thought specifically about whether what kind of an action or contribution this group could make. I think there may be some areas in which we could make some specific and targeted suggestions that might be helpful. Again, I think it is one of those things we can't take on independently, but it is an extremely important way in which genetics is going to have a particular impact and particularly in the arena of health disparities.

Just even the issue of the use of the word "ethnic," just everybody remember that the word "ethnic" specifically excludes biology. The word "ethnicity" and talking about someone's ethnicity excludes biology. That is the definition of the term. So, we are just all over the map in terms of how we are thinking about these things.

DR. MC CABE: I think that was part of Reed's comments was that ethnicity may clash with the biology as we begin to learn the biology and, yet, if we are talking about the

risk of disease, we may be talking more about the biology than the ethnicity, though they can both come into play.

Judy, I would suggest from this discussion that you really do your group focus on health disparities in genetic testing and genetic services. That is a very broad issue. There are a lot of issues that have been put on the table, as well as others that we haven't discussed here that one would have to consider. But really try and see where a focused recommendation to the Secretary from this group could have impact.

I would suggest that you begin perhaps by talking to the government agencies that are represented here to see what are they already engaged in regarding health disparities and specifically as they might relate to genetics and then try and ascertain what other activities are ongoing so that we could then see how we could focus our recommendations to the Secretary.

DR. LEWIS: This has been very, very helpful. Thank you all very much.

DR. MC CABE: Thank you all for a very active discussion. I am very pleased with the progress that our working groups are making.

We will break now for lunch. The lunch for those who are on the panel is in Conference Room 9. There is a cafeteria down on the first floor in the A Wing.

[Whereupon, at 12:00 noon, the meeting was recessed, to reconvene at 1:00 p.m., the same day, Thursday, November 2, 2000.]

A F T E R N O O N S E S S I O N [1:00 p.m.]

Public Comment

DR. MC CABE: This is our public comment period. So, we will have one public comment now and then we will have time for public comments later in the afternoon. Again, if anyone has any wishes to register for public comments, either today or tomorrow, please let Sarah and her staff know.

Dr. Mike Watson is here representing the American College of Medical Genetics. Mike is currently a professor at Wash U. in St. Louis, but is in the process of moving and will be the first executive director of the American College of Medical Genetics.

He is going to make some comments about reimbursement and other issues.

Mike.

DR. WATSON: Thank you for letting me do this today and sort of pre-comment to what you are going to be talking about tomorrow because I do have some areas of interest in reimbursement issues in genetic testing and how they are ultimately impacting potentially quality and access of testing.

It is a very interesting issue and it really impacts a lot of different areas of the things that this group has been talking about, surprisingly. In many ways, reimbursement has become in the marketplace kind of environment that Elliott talked about and others have commented on, it has very much become a de facto regulatory system in this country for the delivery of health care, not that I favor that as the preferred approach to controlling use, but it is certainly in a highly business-oriented marketplace, as our health care system has become, one of the tools that is out there right now.

I actually think that there are pieces of it that could be useful to your deliberations in thinking about how you are going to actually know whether or not anything you

have talked about certainly for the two years that we did the Task Force on Genetic Testing and now the Secretary's Advisory Committee, whether or not you actually made any impact at all because as of right now, there is no way to monitor what goes on out there in our laboratories and in our clinical services.

Virtually all coding for genetic testing is generic. All I do when I do a test is say I did sequencing or I did a hybridization-based assay that has virtually no relationship to the disease I tested for. Sometimes there is a clinical indication of a phenotype of a patient. So, I think one of the things you can certainly look at is the way we code within the billing and reimbursement system for the tests that we do and the services we provide to patients and bring greater specificity to genetics.

You may not be able to deal with every genetic disease as an independent entity by name. Perhaps you can. They have certainly managed to do it for every bug known to man under infectious disease testing now. But clearly you can develop a system whereby those genetic indicators, is it done for diagnosis, is it done for carrier testing within a family, which is essentially an extension of a diagnostic type of test, or is it a carrier test within a population for screening.

And beginning to think about the coding systems that are traditionally used, to tell a reimbursement body why they should pay for doing the test, that the test was truly justified for whatever indications they accept, I think you have got a long way to both allowing the payers to know whether or not something should have been paid for or not and having a mechanism of actually tracking what is going on in the country with different kinds of genetic testing.

So, both the CPT side, where we talk about what we do and what the disease is that we are testing for and the ICD coding side, which is incredibly deficient in genetics right now, can both be greatly improved to help people know what we did and actually look and see what is going on in the country relative to the tests we are providing.

There is another aspect of reimbursement, which is the licensing and those kinds of issues that relate to reimbursement and there are aspects of licensing, which are ultimately beginning to impact access to testing and ultimately access to certain levels of quality of information and interpretation of results. I think within certainly on the laboratory side of the business, we have codes now and everyone agrees that we have to interpret our tests so that a non-geneticist physician understands the results of the genetic tests done.

As of now, about 40 percent of the labs in this country are directed by Ph.D.s. Under HCFA, they have converted that reimbursement to a professional component, which is only to a physician. So, those people who are board-certified in genetics, trained to provide the service and interpret the tests that they are doing are actually unable to be reimbursed for doing the interpretive piece of the testing that is required or is certainly recommended by anybody who looks at genetic tests.

So, I think ensuring that there are either licensing mechanisms or other ways to be sure that people who are trained to do certain things are able to actually do those and be reimbursed for them is going to be important in ensuring quality of services. The same thing exists on the genetic counseling side.

There are a number of different ways by which a genetic counselor might be reimbursed for their services, but there are often done as a linkage directly to a physician or as part of a program within a hospital. There are a couple of ways by which they can reimbursed, but it is clear that they cannot independently reimburse and it is probably one of the reasons a recent paper in genetics and medicine looking at counseling showed, I think, about 80 percent of counseling was being down in other specialties and 80 percent of the people doing it acknowledged that they didn't really know what they were talking about. That is a fairly frightening prospect. So, if we want to ensure the delivery of good information to patients, I think we need to look at ensuring that those most qualified or certainly best trained to provide those services are built into the system that exists out there because genetics wasn't part of the

system as it developed. We are just coming in now and are very poorly understood or acknowledged within the billing and reimbursement systems as they exist. The fact that we also do carrier screening in populations means that we are not just dealing with Medicare and HCFA, but have other bodies of government, which decide whether or not certain screening programs in populations will exist either at state or federal levels.

I think it is going to be important to look at those because certainly when we think about the value of genetics and disease prevention, that it is going to be in those kinds of areas where reimbursement is going to be increasingly important.

Now, I could also say that the American College of Medical Genetics recently finished a cost analysis of genetics testing services all over the country. We found that within public payment systems -- well, across the board much of our money comes from public payment, but across the board, we are reimbursed on average 20 percent of our cost for providing tests, which is making it very, very difficult for laboratories to do the kind of work needed to go through the validation and other things that are clearly needed to provide a high quality service to a population that doesn't understand what we do very well.

It is going to impact the laboratories to develop these materials and make them available. So, I think it is important to begin to really look at how a true cost of tests and whether or not the system adequately acknowledges what the cost of tests are because it is either going to limit access or limit quality if payment is so far under actual cost of providing services that it becomes a problem.

Now, on the other front of oversight of laboratories, I want to make sure that -- one of the problems I think that can happen in regulatory oversight is that -- and I see it all the time in these kinds of groups, saw it on the Task Force -- is that we have overgeneralized what we call genetics and genetic testing and that could quite a problem.

As I see it, we are rapidly moving to a point where we have sort of a two-tiered testing system. The first tier is going to be pretty straightforward stuff, where you have a "yes"

and "no" answer. Do you have this mutation that is known and the clinical information about the mutation and its impact are known. That is going to be a "yes/no" question. Is that mutation there or not? That is much more amenable to oversight than is the much more complex level of genetics that will always exist, I think. That is if you use cystic fibrosis as an example, 80 percent of the mutations we know about are rare or private, meaning they only exist in a very few people in the world or only in one family or one person in the world, which means that they are not going to be on a list of known mutations that you can ask a "yes/no" question about. They are going to be sitting there as a scan of a sequence of a gene, where someone is going to say, now, is that kind of a change likely to be disease related or not.

That is a very different kind of genetic test. Cytogenetics is very much the same in that it is highly subjective. There is a lot of standards that are developed, but it is very hard to regulatorily oversee cytogenetics because it is probably a bit closer to radiology in the way it works in a laboratory than it is to the classical laboratory testing with "yes/no" answers.

Certainly, tandem mass spectrometry and newborn screening is another area, I think, it is a place where newborn screening does need to be revisited to some extent because that technology certainly changes the perspective. The amount of information that comes out of tandem mass spec and the number of peaks about which we know absolutely nothing but on which occasionally people will try to interpret something are significant and I think is a place where we do need to think significantly about that technology in newborn screening.

These two tiers can also impact the way services are going to ultimately be accessed. The "yes/no" answer is the one that we are going to be seeking regulatory approval for and it is going to be the cherry picking part of genetics, where it will be straightforward and we will be able to ask the question and get the answer. But it will limit the access to the much more complicated lab services, which have traditionally been underwritten by that more straightforward easy test.

So, I think if you think about it in those two tiers, that we will certainly be better off. One last comment, in the department of rare diseases, I think it is going to be equally important that you broaden your perspective from disease to mutation because many, many mutations are going to be very rare in some ethnic groups and may not be accessible in the tests, so the mutation itself can be a rare entity to get tested.

I may develop a test where that mutation is the only one I get asked to run a test for and will be considered incredibly rarely done. But I think you need to broaden that perspective away from disease to the individual mutations because with now over 900 in CF alone, many of those will never be tested for and we will need some sort of incentive to ensure that they don't get left behind in the process of developing these tests.

Thanks.

DR. MC CABE: Thank you.

Any questions for Dr. Watson, comments?

[There was no response.]

Okay. Thank you.

Now, are we set with our technology? Okay. Good. So, our next agenda item them is a brief report -- we will come back for public comments -- is a brief report from Dr. Charache on the activities of the Clinical Laboratory Improvement Advisory Committee. As you know, Dr. Charache serves as a liaison between our Committee and the CLIAC. Today she will be reporting on the last meeting of the CLIAC and the status of the CDC's request for public comments on the notice of intent to add specific genetic testing provisions to CLIA.

Update from CLIAC

DR. CHARACHE: This has been a technical roller coaster. It was wiped out last night on my computer and this morning on our setting up. So, I hope it is worth having made the slides.

What I am just going to emphasize are the topics that were covered at CLIA that are related to this group's interest in genetic testing. So, I am going to do three things: Review the comments that were made on my report and that of others on the activities of this group and particularly the amended report with the diagram of possible strategies for assessing genetic tests in terms of their scrutiny level and review the comments on the notice of intent and waive tests.

The review of the report, there was a great deal of discussion about the difficulties of oversight of home brewed tests and these were largely volume-related and the question of what is a test, does every individual home brew have to be reviewed separately? Certainly can't be reviewed by diseases. In looking at this Committee's work there was a focus on the test scrutiny emphasis and noting that these did not include consideration of laboratory complexity.

All of the decision, whether the test was Level 1 or Level 2 were based on medical or social decisions as opposed to our consideration of whether this test was highly complex and would ordinarily go into a different category because of the technology, as opposed to its disease name and the implications of that disease state.

So, it was recognized that that second concept has to be entered into scrutiny, which is the considerations that are usually given to test complexity or uniqueness of technology in categorization. There was a lot of concern with the level of scrutiny diagrams, but they were based on issues that have already been discussed here primarily. They were based on the use of test volumes and there were a lot of considerations there of the volume issue that caused problems and then the issue we talked about this morning about diagnostic versus predictive testing.

The CLIAC was very impressed with the testing of this diagram that was done, which we mentioned earlier also, by the Genetic Forum. So, there is a great interest in seeing that reviewed, but it is along the lines that this Committee expressed support for this morning.

Background for the Notice of Intent. As you know the Task Force report was in 1997 at the same time CLIAC was presented with the question of genetic testing and elected to investigate it further. The Genetic Working Group was established that same year and it reported its findings to CLIAC in 1998. In 1999, the Notice of Intent was drafted. Now, it had a long birthing process and this Committee helped a lot by suggesting that it be speeded up through the interstices of the various groups that had to assess it.

In May it was published and it was reviewed at our last CLIAC meeting. I am not going to cover all of the comments that came back, but give you an overview of their concept because our next activities of CLIAC will be to address the issues that were raised.

There were three major groups of issues that were incorporated in the Notice of Intent. The first was the definition of a genetic test and the definition is that which with some word changes was approved by this Committee. I am going to mention some of the comments that were received on that definition.

There was a question of whether genetic tests require a separate oversight category, like cytopathology has now or whether the rules that apply to any high complexity test would apply to genetics. So, that was put in there. Then there were specific proposals for added oversight and these recommendations were organized as they would be assessed in laboratory oversight and practices, which was in pre-analytical, analytical and post-analytical phases of testing.

Examples of what was in there for specific modified oversight included pre-analytical phase testing and I have just listed some of the topics on which people made comments. But they do include confidentiality, informed consent, test ordering practices, position of required information before you run a test, specimen procurement issues, transport, laboratory assessment of the appropriateness of the test, so you don't run a test on the wrong category of individuals.

There was also in the analytical phase, the things we usually think about, but also specific aspects of issues such as proficiency testing because there are no commercial proficiency tests for most of these and there were surrogate proposals made for frequency of testing and nature in testing and so on.

Finally, in the post-analytical phase, the report format, the content required in a report and the detail required, the interpretation of results, methods of result return, and so on. So, this Notice of Intent had a great deal of questions raised in it in which the nature of the question was defined and then posed.

The response did not include a large number of respondents. There were 57 respondents, who made 748 comments. But they did include the relevant organizations. All of the major private organizations that are concerned with genetic testing came in along with others. So, this represents a small but substantive group that commented on the points that were raised.

These are the issues that received the most comment. The question of the definitions and the categories of genetic tests, the role of the laboratory director -- and I am going to come back to that and particularly as it pertained to their need to document the clinical validity of the tests they offered -- who could order tests, the documentation by the laboratory of informed consent, the suggestion the laboratory has to make of counseling available to not necessarily on site but who can help understand the test, personnel qualifications and responsibilities.

A couple of general comments: There was a lot of support for the specialty of genetic testing being separately designated. There were several points made in the definition, which would apply to this Committee's definition as well. There was a recommendation for separation of molecular and cytogenetic, which this group has supported.

There was a lot of comment on excluding non-heritable diseases and only addressing heritable diseases as genetic tests and there was a question on the part of several

groups about including biochemical categories, which was questioned. So, these were the issues that were picked up in terms of the definition.

There was a lot of comment on the post-analytical and specific requirements for answering questions and the role of the counselor in that responsibility, but I think a lot of the issues raised was the change in the role required for the laboratory and the laboratory director in the recommendations for oversight at the laboratory level.

Now, specifically, the laboratory and its director would be responsible for documenting that informed consent had been obtained. This is a big statement. It means that they can't do the test if they haven't checked the box on the requisition that says that they had actually asked the patient for consent to do the test. So, that places the laboratory, particularly the large commercial laboratory, in a very different position than they are in now, which is to do a test and then just say, well, that was the clinician's responsibility to get informed consent and we don't have to oversee it.

So, that is a big change in responsibilities. Not performing the test, if the population is not appropriate for that test. That means you need to know what the population is that is being sent in. Responsibility for not performing a test if it can't be interpreted because you don't have the information you need or the test has not been clinically validated and a role in documenting clinical validity.

So, these make a very major change in the role of the laboratory director and his relationship to the clinician, who orders the test. I am not going to go through some of the answers, but informed consent, some organizations thought that CLIA was the right place to regulate this. Others thought it was not the right place to regulate it and there were a lot of questions for the wording that was used.

Similarly, the question of whether the genetic counselor should be made available by the laboratory and some thought that it should be -- eight organizations thought it should be made available for health care providers. Some thought they should also be able to do

genetic counseling for family members and others not. So, there is a lot of issues here that need to be sorted out.

Now, that is all I am going to say about the kinds of responses that came back from the Notice of Intent. They were comprehensive. They were all over the map and they have to be sorted out.

I am going to make one other comment on the third issue, which is the waive testing issue that concerns CLIAC very much and just to make you aware of the issue and that pertains to a very different topic, which is waive testing. According to CLIA, all tests are placed in one of three categories. Then the category governs the permissiveness of how that test can be performed, whether you need to have a supervisor on site, whether it can be done by a high school student, but they are divided into high complexity, moderate complexity, and waive tests.

If a test is waived, there is no CLIA oversight or monitoring. It is withdrawn from CLIA. So, if you have, for example, a waived genetic test, there would be no oversight after the test had been categorized. A test now has had a changed definition of what tests have to be waived and they are waived if one or the other of these two factors apply; if it is easy to perform or if it is unlikely to cause harm if the answer is incorrect.

Now, until the FDA Modernization Act, this was an "and." It had to be both easy to perform and no serious harm if it were performed incorrectly. Now it is an "or," which means that you have an easy genetic test with a colorometric endpoint that could be done by anybody, it doesn't matter whether it has medical or social implications. It would fit the waive possibility. It doesn't mean it would be put there, but it certainly can. And it is supposed to be waived if one or the other of these applies.

So, I wanted to call your attention to this, that there is a new and potentially permissive policy under consideration, which concerned the CLIAC group, which would be a more permissive definition of whether a test is deemed to be accurate. For genetic tests, this

would impact on the ability to improve the oversight as the Notice of Intent and so on would not apply.

Now, this is still under consideration. I am calling it to your attention because it is under very rapid timeline consideration in that one test was released a week or so ago with the new and more permissive possibilities. Now, the next steps, which should be here, and this is the final slide, the CLIAC appointed a genetics working group to address all these issues that were raised by the Notice of Intent and make recommendations to CLIAC on this in preparation for proposing specific new regulations.

They also appointed a working group for the waive testing and a letter was drafted for the FDA requesting that they hold implementation of the new waive testing policy until CLIAC had had a chance to discuss it. This is now being held until that whole policy is formulated a little more securely.

Then both of these two groups will report to CLIAC for their next meeting to advance consideration of these disciplines. So, those were the major aspects of the CLIAC meeting that pertained to this group.

DR. MC CABE: Thank you. On our schedule, we don't have discussion after each of these. I think we will hold that until the end of the day, unless there is something really burning that anyone has.

Let's move on to update on the CDC's GenTAP activities. We are going to hear from Dr. Muin Khoury for an update on GenTAP, the CDC's focal point for efforts to enhance data collection around genetic tests and genetic testing process.

He will be followed by Dr. Joe Boone, who is assistant director for science, CDC Division of Laboratory Systems, who will report on the meeting of the CDC Genetic Laboratory Forum.

So, first, Dr. Khoury.

Update on CDC's GenTAP Activities

DR. KHOURY: Let me first correct a misnomer. There is no word GenTAP that exists anymore. GenTAP is sort of a transient acronym that we developed back in June or August, when I addressed this Committee. It has been replaced by the word GAP or Genetic Testing Assessment Program, in order to close the gap between gene discovery and public health.

But I will barely have time to talk about any of this stuff today, so what we will do between Joe and myself, we will give you a quick update about our initial data collection efforts that started with our two model projects that led into the funding of a cooperative agreement for a model system for how we collect data. Then Joe will give us a brief overview of what the Lab Forum had some input on the SACGT test classification. Then I will come back and discuss a little bit more in-depth the suggested revisions to the flow chart model for classification.

You all have, I think, a copy of these slides in your packet. The first thing I would like to say is that at the end of September, we funded a three-year cooperative agreement grant to the Foundation for Blood Research in Maine to help us move to the next level of coming up with a model system or an approach for how we evaluate genetic tests. That group has a long track history of evaluation of genetic technology and I think will make a fairly substantial impact. It is a three-year project and has the following purposes. They are all on your packet.

Develop a model system for assessing the availability, quality, and usefulness of existing data on genetic tests. That would be the first step.

No. 2, develop a model approach for collecting, analyzing, disseminating and updating the information on genetic tests and then apply it to up to ten conditions over the next three years. The first year we are going to focus on our efforts to finish up the two pilot projects, which we started last year on cystic fibrosis and hemochromatosis, plus an additional third one, which would be Factor 5 Leiden and then move on to other things.

Basically, the way this model system works is that there is a core research group that is composed largely but not exclusively by members of the Foundation for Blood Research, Jim Haddell and Glen Palomocki, enriched with some people on the outside, like Wylie Burke and Nancy Press, sitting in the audience here, that is a core advisory group that is going to help them sort of evaluate how the project is moving along and then the actual work will be carried out by disease-specific core groups that people who are experts in the three areas that we have talked about, plus consortia that involve both the private and public sector.

Then there will be a lot of review and input from different groups and we hope to keep SACGT informed and engaged and give us input over the next couple of years.

The first thing, at the center of this model system, as Wylie said this morning, and what I will be discussing very briefly is the beginning of the implementation of the stuff that Wylie talked about because I would like to dig into a little bit more specificity in these issues and the test disorder information is that first step, which we call intended use because all of the information on analytic validity, clinical validity really are intended use-specific and for one disorder or one condition, you can have several of these report cards that Wylie put up this morning, depending on what the test is intended to be used for because these parameters will change.

The purpose of the test, the specific outcome that is going to be measured, the target population, and then the methods, the laboratory methods that are available for that intended use -- just a brief example, if you look at CFTR, for example, you can have one intended use in newborn screening for cystic fibrosis, another intended use being carrier testing for CF. A third intended use might be testing all people with azoospermia or infertility as part of a diagnostic work up or chronic sinusitis as a recent article in JAMA came up with at the outset of genotype/phenotype correlation.

We had one preliminary meeting with this group last week actually and the group began to define the task at hand and I would like to run through four slides, one on analytic

validity, one on clinical validity, one on utility, and the ethical component. By the way, the group calls this project the ACE Project so as not to repeat these cumbersome words all the time.

For each one of these items of data, they have identified -- so, trying to begin to define the tasks at hand, sometimes it is difficult to define these things because people use different language. For example, the word "detection rate" means different things for different people, and "false positive" and they have begun to put order into the classification of analytic sensitivity and specificity in relation to a specific genotype, which has some counterpart measures in terms of detection rate and false positivity.

For each one of these what the group will be doing is not only reviewing the data on the analytic validity but reviewing the data in the real world, what we call critical factors, that would affect the way or the ability to measure the analytic validity, things like the precision of the test, quality control, robustness, genotype prevalence, or population subgroups, and I don't have time to go into the definition of each one of these things.

Sometimes you have an analytic validity that varies from day to day, for example, or from assay to assay or it is not repeatable over time or there are no procedures to do that. But we can discuss some of that as we go along.

Moving on to the clinical validity side, again, the definitions -- the usual definitions of "sensitivity" and "specificity" now in relation to a specific genotype, but then you introduce the basic concepts of positive and negative predictive value and what they mean in a clinical sense. As Wylie mentioned this morning, it is very difficult sometimes to put your arms around tests that are going to be used predictively on the long run and trying to measure penetrance or age-specific predictive value if you will and the critical factors there are obviously the prevalence of the disorder or outcome, which will affect your predictive values in a big way, the population subgroups, and genotype and phenotypes correlations and modifiers.

I think this is something that Reed mentioned this morning, the presence of gene environment and interaction is a major deal, which can affect your clinical validity measures.

One case in point, for example, the way you look at hemochromatosis clinical validity might be different if you take iron or if you don't take iron or if you drink alcohol or you don't drink alcohol.

Of course, clinical utility is looking at improved clinical outcomes after testing. We want to see evidence as to the benefits and risks of testing and there are, obviously, the critical factors there, whether an intervention exists, how effective it is, the natural history of the condition, all the financial costs, pilot trials, education, facilities, quality assurance, monitoring, and program evaluation.

So, clinical utility takes on different dimension than just clinical utility in a research setting but clinical utility in the real world, which is really what we are after. Then the ANSI data, which is probably the toughest part of this project, which we hope that Nancy Press can begin to make a substantial impact on this is how do we from the literature begin to define the occurrence of all these ethical, legal, and psychosocial outcomes in relation to testing, whether people get tested or not, things like stigmatization, discrimination, et cetera.

The critical factors, of course, there are the existing safeguards and impediments that exist from a variety of settings.

So, I would like to move on to the second part of this presentation. Joe will give us the input of the Lab Forum and then, hopefully, we will have some time to digest all of this into a revised model.

DR. BOONE: Thanks, Muin.

There were three purposes for the Laboratory Forum that we held in September. One was to review the CLIAC Notice of Intent comments and the plans to implement a genetic specialty. The second was to review and apply the SACGT test categorization schemes to specific tests, and finally to determine whether or not there was any need to modify that scheme.

What I would like to do is to illustrate the process very quickly that we went through in that Lab Forum. We did pick eight tests to look at. These are the tests that we looked

at. Some of these tests are predictive; some are diagnostic; some are presymptomatic; some are for screening tests. So, we tried to pick a group of tests that we thought were at least representative of the field out of all the tests that could be looked at.

To give you an example of one of those processes, we looked at the cholesterol ester transfer protein, which is basically a pharmacogenetic testing because you are looking for drug therapy for coronary artery atherosclerosis and what we provided this group with seven different parameters about each of these tests. We provided them with a clinical description of the test, the test definition, the purpose of the test, whether it was predictive or diagnostic, whether it was stand alone or whether it was an adjunctive kind of test, what the prevalence was, whether there was an intervention in the event that there was a positive test finding, and also the detection rate.

With that background, they were given a certain amount of time to go through these tests and this is an example of the test volume for this particular test was viewed as being high. The population was not a classic population because you are looking at a subpopulation of specific patient populations.

This test was primarily diagnostic to guide the selection of drug therapy. Therefore, the overall decision was Scrutiny Level 1 test. It was a very quick procedure through that process.

In terms of our findings, we agree with a lot of the comments that were made earlier about the problem with definitions. That was one of the biggest problems we had was trying to see whether we had an appropriate definition of the tests that we were even considering.

One of the people says, well, what is a test, what is this test that we are even talking about and the fact that we felt like we did need to include not only the clinical aspects, but also some of the analytical aspects in a consideration because a test is not the same test, depending on the analytical complexity.

So, the first suggestion we would have is that the technical analytical requirements may need to be considered since they do impose an additional risk beyond the intended clinical use. We have already talked about test volume. We have talked about the population needing definition. We also talked about the last issue of diagnosis versus predictive. So, I won't go into that because you have already covered that, I think, quite well.

About the only thing else that we did talk about was karyoscreening perhaps needing to be treated separately. Other factors that were mentioned were the fact that if you were using a test as you usually would, as adjunctively, at least starting out, that there may need to be less scrutiny for that, that social risk probably did need to be at the top of the list, rather than at the bottom of the list as someone has talked about earlier.

So, we would suggest that you consider the risk first and not last and that we felt like that the process needs to be flexible, quick, and address primarily the risk concerns that you have for those particular tests.

I think we certainly agree with the comments that were around the table today and because of all of this interaction, we certainly tried to drive ourselves toward another model, which addresses some of the points that I think have been raised earlier today and Muin is going to cover that.

DR. KHOURY: So, based on the input from the Lab Forum and many other discussions, we had great collaboration between our office and the Division of Lab Systems. We had two people work through the SACGT model and came up with the thing that you saw earlier this morning, which I wanted to take a few minutes to go over at this time. You may want to have in your hip pocket what SACGT recommended last time.

The first step that I think everyone agrees on which is basically a pre-model thing is looking at the analytic side of things. You can have a clinically indicated test, but if you have either a complex test or a lousy test, I think that first step has to be pre-modeled to anything.

I mean you have to have the ability to reject a test based on its poor analytic performance. I will not touch that any further.

But if it meets that first test, I think the next step would be perhaps to insert the social stuff at the beginning, as many groups said. The Lab Forum said that. I think many alluded to earlier. The problem with it is how do we define that in a way that doesn't push everything to Level 2. In some way what the SACGT has done is to try to make the definition of social issues operational enough by using some of the other criteria so that to distinguish between Levels 2 and 1. But the problem is I think there is so much noise around the edges.

You might want to consider having that social step at the outset, but if we don't, then the next level would be to replace the volume of testing parameter by the combination of the intended use in a population setting combined with the prevalence to get indirectly at how much test volume there is. Let me just warn you, as we go through this suggested modification, we were approaching this from a public health angle.

Because right now there are 800 test that are on the market and there will be many more for the years to come. As we want to begin collecting data on tests and testing, we can't really collect data on everything , we wanted to dovetail this regulatory approach to classification and come up with a list of tests we wanted to focus on from a public health angle So, that is why the population use came at the top of the chart, things like newborn screening targeting subsegments of the population will go forth in my mind, regardless of whether the disease is there or not because everybody in a population or subsegment of the population will be tested. These are new ones now. I mean, we are not just looking at PKU anymore, but any new tests that are used for population testing will be automatically shifted in Level 2 for discussion.

Now, followed by a prevalence and you can argue about whether we should use 1 in 10,000 or 1 in 20,000. We can refine that. I think the traditional definition of something rare that is 200,000 people or less or there could be some other definition, which translates into a prevalence of 1 in 20,000 if we use 400 million people who live in this country. We could agree

on something that would make some initial cut of rare versus common. We chose 1 in 10,000 and those that are rare will be either shifted into Level 1, which is what the initial SACGT paradigm said, or as Mary suggested today maybe with some further discussion with the FDA, could be a level all by themselves, sort of this humanitarian device exemption. But for now, let's put them in Level 1. Now, if then if you are dealing with a common disorder, there the last step will be the intended use and, again, we use a primary split of diagnostic versus predictive, although we heard from Wylie this morning in another discussion that this might be problematic. But the way we were approaching this is saying if somebody is already sick and you are using that test to diagnose them rather than predicting the future risk of disease, then that goes into Level 1.

Anytime you want to use a test to predict the future risk of a common disease that becomes into a Level 2 type discussion. This is a simplified diagram, but we didn't want to stop there because we wanted to test it in the real world and we barely had time to do this in the last two days. We had two people work on it and it is reflected in this diagram here, which you also have in your packet. We went over the genotype database plus the New York State -- some of their materials and tried to apply this to the 800 or so tests. This is what we came up with.

I already see a couple of things that can be improved on; for example, congenital hypothyroidism is not a genetic test. We can throw that out. But if you look at the Level 2 at the top, you will see a bunch of things for newborn screening, a bunch of things in the panel for karyotesting or Ashkenazi Jewish panel and on Level 2 down in the predictive sense you will have some of the cancer genes and the Factor 5 Leiden.

The one thing I didn't mention is that in the SACGT classification you have a further box under predictive, which tried to ask a series of questions, intervention proven or nonexisting low predictive value, significant potential medical or social risk. We decided that in order to answer these questions that had become so complicated from a regulatory scheme and so

we said if we throw out that box, what happens if we put every single predictive test in Level 2? Will we basically overrun the ability to deal with Level 2?

If you look at this list, which I am sure can be modified some, we find that no more than 5 to 10 percent at the most, if we follow this scheme of the 800 or so tests that currently exist, fall under Level 2 review. I mean, we might argue about specific ones and actually some of them are a collection of tests. For example, the fatty acid absorption disorder

– that is not one test. You can think of M-CAD and L-CAD and some of the other ones, but really the issue is rare versus common and that makes it the big classification issue. If you can put the rare in a separate category on that step, you will see that not too many of them will fall into the Level 2 review.

Now, with the two caveats is that this binary system of diagnostic versus predictive needs to be improved on because you have the prenatal stuff and the pharmacogenetics. I am not so sure it folds neatly under either diagnostic or predictive because although you are sick, but you are predicting outcomes or treatments of illness that may be affected by the way you take medications or not. So that pharmacogenetics is a little bit outside the traditional box, although from what you heard from Joe, the Lab Forum decided to put it in Level 1 because they viewed it as a diagnostic test.

So, this is sort of work in progress and we thought to bring it to the table here for further discussion because I think it dovetails with everything else that we heard this morning.

Questions?

DR. MC CABE: Yes. Fairly briefly, though, because we are running behind and I want to have time for public comment.

DR. COLLINS: Just a quick question.

If you ran this same set of a hundred tests through the original protocol, as far as the original flow chart, you actually end up with different outcomes. Even though the flow chart is organized differently, what is an example of one that would --

DR. KHOURY: The first thing, you get stuck at the top of the other one. You don't know the volume of testing. That is where you get stuck. Is it more than for x number? If you choose 4,000 -- I mean, it is easier to get a prevalence data of the disorder than the volume of testing. Then the second hiccough would be down at the last box trying to define proven or nonexisting intervention or low predictive value or significant potential risks. So, we are saying that -- let's not ask those questions. Let's put them all in Level 2 and see what happens. So, presumably, some of those will go back to Level 1.

But I am not sure that they do really. I mean, alpha-1 antitrypsin, APO-E, breast cancer, I mean, you might argue around that. But assuming a new test comes to the market today, what we are saying is that Level 2, as part of the Level 2 review, you ask those questions, that they become imbedded in a Level 2 review, rather than you ask those questions first, just put them in Level 2. I think we need to ask those questions and then if the answers are okay, then you just push it through very quickly.

DR. MC CABE: We are going to discuss the model later in the afternoon, so I don't want to get too deep into it now.

DR. BURKE: My brief comment at this point would just be the predictive versus diagnostic -- this is a logical simplification but the predictive versus diagnostic is a crucial issue. I just want to register disagreement with CTPB being a diagnostic test and I also want to register disagreement with the idea that we could define diagnostic tests as tests in people with clinical symptoms. Because I think there are some circumstances where tests could be legitimately considered diagnostic in an asymptomatic. I know we will be able to discuss that later.

DR. KHOURY: Just one quick comment.

I think if we don't get hung up on definitions and we try to say what the intent is because that branch there can encapsulate both diagnostic, predictive, with some of the social issues. So, for example, prenatal diagnosis, it might be diagnostic but if there are enough social

concerns, you push it into Level 2. So, I am sure we will come back to further discussion but I don't disagree with you.

MR. HILLBACK: I will defer to that later discussion because it is all the same issue.

MS. BEARDSLEY: I need to say one thing because I won't be here later.

In looking at these flow charts, I was struck by one thing and -- those tests should have a high level of scrutiny. Yet, I am having some difficulty matching it up to any charts that we have seen because I think the reason for that, at least in my mind, has to do essentially with the finality of the intervention not with the kind of testing.

What that is saying to me is that I think that trying to establish criteria is really important but at the end of the day, there is going to have to be some flexibility. We have to look to FDA to exercise some discretion here and in thinking about it, we have to be very clear that we are not -- these are flexible.

DR. MC CABE: Thank you. With that, we will move on to the FDA.

Dr. Steve Gutman is director of the Division of Clinical Laboratory Devices of the FDA's Office of Device Evaluation. Steve will report on a meeting the FDA held last week with professional organizations involved in genetic testing.

Dr. Gutman.

Report on FDA's Professional Organizations Round Table on Future Oversight of Genetic Tests

DR. GUTMAN: FDA held an inaugural meeting last July in which the agency invited in members of professional laboratory associations. This was viewed by our work group as part of an organizational-wide initiative to increase our outreach efforts and to look for leveraging opportunities whereby the agency would work collaboratively with outside stakeholders to advance its public health mission.

This newly constituted group, which we informally call the Professional IVD Round Table, paralleled an interactive group of FDA scientists and members of industry that has been meeting continuously over the past five years. In fact, both groups are now meeting with the same basic objectives, one, to allow FDA to communicate to stakeholders updated information on its work activities; two, to allow those stakeholders to either praise or criticize us for those ongoing activities and, three, last but not least, to seek collaborative projects in which we can interact with first industry and now with professional groups to work together to meet goals of mutual interest.

The industry-based IVD round table from the agency's perspective is a particularly successful model to emulate. We have worked with this group to develop educational programs, yearly educational programs for sponsors unfamiliar with our review processes and we have had educational programs actually directed from industry to FDA to explain to us new technology or new techniques or promising advances from their perspective.

We work collaboratively to both streamline and enhance some of our review policies and we have actually with industry done the unthinkable; that is, developed guidance documents collaboratively. So, we have had a variety of pretty successful interactions through the auspices of the IVD round table.

The July meeting with the professional groups was entirely exploratory and informational and FDA invited every laboratory-based group we were able to identify, both large and small, with both scientific practice and, frankly, political agendas. We got CDC and HCFA to help and we even invited the group that was in the process of directly a lawsuit against HHS to show how inclusive we were.

In the course of the first meeting, we sought one or more of the attending groups to take ownership or the secretariat for this activity, one, because we wanted to pawn off the work and, two, because it allows us to be a little bit more administratively flexible in terms of what needs to be posted in the Federal Register and how we interact.

The topics that were of particular interest at the first meeting of the round table actually were focused on an issue that Pat raised with you, the CLIA waiver process. There was a lot of interest in reimbursement that was kind of peripheral to us. There was a lot of interest in our ASR rule.

Early this fall, the Association of Molecular Pathologists approached the FDA and offered on an interim basis, not a permanent, but an interim basis to take administrative responsibilities for this new professional round table. A second meeting date was established and an agenda set up that focused largely on FDA issues being raised by SACGT. It was important to us to make sure it was FDA issues being raised by SACGT because SACGT and the CDC Forum and the CDC CLIAC genetic subcommittees are, in fact, dealing with other issues.

We wanted to make sure that we were on a focused course. FDA was frankly enthusiastic about this offer from AMP because we thought it was a good faith effort by a professional group to take leadership in helping us meet one of the charges that SACGT has put on our door, which is to look for collaborative methods of working with outside groups to consider new oversight models. So, we were frankly flattered that they were interested.

The October meeting did, in fact, take place the week before last. Not surprisingly, given the more specialized agenda that was put together for the day, attendance was much more selective and small at the second meeting than it was at the inaugural meeting, but from our perspective, it included a reasonable representative selection of both large and small professional groups and those groups were smart enough to, by and large, send people who were oriented to genetics issues.

In fact, we were fortunate enough to even have a SACGT member present; that was Dr. Charache, who came compliments of the ASM as their genetics representative. So, we had a little institutional history present at that meeting.

There was extended general discussion and specific review of SACGT recommendations and the group provided input on things you have already heard about, the

classification model. They provided input on the data template model, which they particularly liked. In addition, there were wide ranges of FDA regulatory options put on the table.

The meeting resulted in an action plan with four items. Item 1 was a somewhat out of the box-based notion that we would attempt to develop a model for paper inspection of laboratory tests for existing home brewed genetic tests, as a complement to existing oversight programs and that that this would, in particular, be targeted towards claims, towards clinical validity, and towards truth in labeling.

There was a recommendation on endorsement of the ongoing activity by CDC and HCFA to enhance existing inspection programs. There was a suggestion that we develop models for review of new tests and, last but certainly not least, there was an endorsement of the long-term data collection and analysis activities, which have been assigned to CDC as a result of SACGT work.

Items 2 and 4, of course, already within the province of the CDC Forum, although this group officially, in fact, voted and asked that I transmit our enthusiasm for having CDC continue and to report back on their activity on Items 2 and 4, and for Items 1 and 3, it was decided to set up working subgroups on an exploratory nature. For the paper inspection model, a number of subgoals were identified. Those subgoals included to determine what labeling and clinical validation might be appropriate in a paper inspection model, what process would be applied to this program, what options are available on how and who would administer this program. What scientific criteria would be used in this kind of a program? We are going to develop a list of 25 pilot tests to see how they might actually work scientifically or administratively in such a program.

For review of new tests, the charges were to define a basis for distinguishing old from new tests, to determine the administrative process or processes for review, to determine scientific thresholds and documentation for review, and to establish some pilot labeling templates.

Now, there are a number of caveats to this work. First, this is all going to be easier said than done. Second, that there may be a tricky legal basis to this in terms of figuring out how FDA authority might actually apply.

As my boss has indicated, this may not in a clear and forthright way actually address an important issue that SACGT has raised, which is the research to clinical use transition. It is something I probably will put back on the agenda for both subgroups. There is an obvious need to coordinate with the work of others. It is obvious that we need to have the same or a similar template to the template that CDC would be using in its long-term data gathering activities.

In fact, I think Wylie has already done the work for us. She has given us a mother template off of which we can all work and, in fact, it probably needs some additional specificity for certain product lines, but I would be surprised to see fundamental intellectual changes in the template as it now exists.

We need to figure out how and in what manner classification would actually be done and what impact it would have on either of these two review modes. So, there is a lot of challenges. What was also put on the table at this meeting discussing genetics testing was exercising existing legal authority and a first step that FDA might consider frankly is the registration and listing of genetic tests and the requirement that genetic tests, in fact, formally be subject to our medical device reporting system so that when there are life-threatening or potentially life-threatening adverse events, they must be reported to the agency and the agency would have an opportunity to interact with laboratories to identify problems.

These caveats aside, the road forward is somewhat exciting. We have scheduled a follow-up meeting in January of 2001. I am certain that all this work won't be done by January of 2001. There have been subgroups formed with very enthusiastic memberships and enthusiastic chairs. Dr. Deborah Leonard is chairing the subgroup for the paper review model and I am chairing the subgroup for the review of new tests.

There is an opportunity here for interactive success and if there is not success, there is an opportunity to learn from whatever failures we forge forward with. Obviously, an important activity here is for us to coordinate and report and make sure we are on the same wave length as SACGT and with the multiple other groups that have a direct and vested interest in this activity.

Thank you.

DR. MC CABE: Thank you for a very concise presentation.

Are there comments, quick comments now and we can follow up with more detail later?

[There was no response.]

I will take the absence of comments to mean that people are -- I know I for one am a bit blown away by how much you have accomplished so quickly. Thank you for moving forward so quickly on this.

I think it will be interesting to see how it proceeds as you get down to the examples, but please do keep us informed of how things move forward.

Any other comments before we move on to the next section?

[There was no response.]

We have no one who has registered with any of the staff regarding public comment. So, without further public comment at this time -- we will have time tomorrow if someone wishes to speak at that time.

Session on Regulations Governing Labeling, Promotion, and Advertising of Medical Devices

We are now going to turn to our session on federal regulations governing the labeling, promotion, and advertising of genetic tests or medical devices more broadly.

These regulations are an important element of oversight of genetic tests and we have wanted to learn more about them and to understand how the FDA and FTC, the two agencies with jurisdiction over consumer protection of health-related products, are or could be applying the regulations to the promotion of genetic tests.

We also want to understand how the two agencies' roles and responsibilities intersect in general and in the specific area of diagnostic devices, how the regulations address off-label use, direct-to-consumer marketing and new technologies, such as the Internet for marketing health-related products.

We are very pleased that two of the leading experts from FDA and FTC, Mr. Byron Tart and Mr. Matthew Daynard, are here today to brief us on these important matters. Following each presentation, there will be an opportunity for Committee members to ask specific questions. At the end of Mr. Daynard's presentation we will ask him and Mr. Tart to join us in a discussion of these issues.

We will begin with Mr. Tart, who is the director of Promotion and Advertising Policy staff, Office of Compliance, Center for Devices and Radiological Health at FDA. The Promotion and Advertising Policy staff formed in May of 1993, is the focal point for all issues associated with the promotion and advertising of legally marketed medical devices.

Mr. Tart has been with the FDA since 1977. He was a field investigator for ten years with the Kansas City and New York Districts. He joined the Center for Devices and Radiological Health in 1990. Mr. Tart has a B.S. in biology and an M.S. in microbiology.

Mr. Tart, thank you for being with us.

MR. TART: Thank you very much.

I have some overheads. I am going to try to give you a general background on promotion and advertising of legally marketed devices. Then in some of the examples, we can look at the genetic test issues that we actually address.

When I was asked to give this talk, I was asked to answer or look at four questions. How FDA regulations govern labeling, promotion and advertising and how in the future they might apply to genetic tests? What the FDA's role is in relation to the Federal Trade Commission's role? Mr. Daynard will be answering that question.

How regulations address off-label use? And there seems to be in the last two questions some interest in if there is any differentiation between direct-to-consumer advertising and professional advertising.

When I do any of these speeches, since we have a rather diverse group in the Office of Compliance and our responsibilities are broken up, I like to give a little run down between us and the Federal Trade Commission. When you look at advertising for medical devices, because of the way the Food, Drug, and Cosmetic Act is written, our agency, the Center for Devices and Radiological Health only has jurisdiction over the advertising.

Now, when we talk about advertising, we are looking at advertising in magazines, television, radio, what you traditionally would think of as advertising, as opposed to labeling. But if you look at advertisings, we have jurisdiction over the advertising of what we call restricted devices. And I will give you a little run down on what that is.

Any prescription device that is advertised, that device that you would get on or by the order of a health care practitioner, those advertisements are really regulated by the Federal Trade Commission. Over-the-counter devices, as are over-the-counter drugs are also regulated by the Federal Trade Commission and the only exception is that the FDA has jurisdiction over how the intended use -- in other words, what the device is actually going to be used for.

If a manufacturer or distributor misrepresents the intended use of a particular medical device, then we have jurisdiction no matter where it is, whether it is an advertisement or in labeling. In the labeling area, for promotional labeling in advertisement, that falls to my group, which is a group of about six people.

If a company product labeling, for example, even in genetic testing, it would fall to what we call the Division of Enforcement. We have one branch within one of the Divisions of Enforcement that deals mostly with in vitro diagnostic products. So, they would be primarily responsible for the labeling of the product.

The investigational device advertising goes to the Division of Bioresearch Monitoring and if there is any unapproved devices, which I am sure you have seen being sold over the Internet, whether it is test kits, et cetera, that goes to what we call the Division of Enforcement.

So, there is a split of duties within the Center. When we look at promotion and advertising, I mean, when we look at off-label use and that is, I think, what we are somewhat interested in here, because if a device is promoted for the use that it is intended use, we really don't have much interest in it. When we look at off-label promotion, we look at statements that are made in advertising. We look at any implied benefits that a manufacturer may make in the advertisement.

If a manufacturer sells a device, for example, that was only approved for use in a very narrow specialty, let's say in heart surgery, that is what the device has been approved to, but in off-label, it is now to be used, let's say, in the brain, if a manufacturer sells that device to a physician who or a group that deals specifically in that area, then we would consider the manufacturer selling that device for an off-label use.

The sale of a Rx device over the counter, if a test kit, for example, is only approved on or by the order of a physician, an Internet provider through the Internet sells it over the counter, then that would misbrand the product. Off-label promotion also occurs when some manufacturers use testimonials. Some patients who have had the device used on them off-label and make certain statements and the manufacturer incorporates that into their advertisement and that also is off-label promotion.

In the web area, connecting to a web site that is known for off-label discussions, that is also off-label promotion and connecting to foreign web sites where many devices are approved, including in vitro diagnostics for uses that are not cleared for the U.S. Of course manufacturers in the U.S. sell their devices both in the U.S. for the intended use they have been cleared for and in the overseas market for the use that they have not.

I was asked what were the regulations in off-label promotion or how we govern these products and when we traditionally take a regulatory action against a medical device that is being promoted for an unapproved use, they use certain provisions in the Food, Drug, and Cosmetic Act and, I am not going to go through all of these, but basically the two charges that we make in any action we take is that the device is either misbranded because it doesn't have clearance to be in the marketplace under what we call 510(k) or they have made a false or misleading statement or they are adulterated because the new use that they are promoting is Class 3. This is a legal issue and they don't have a PMA for it.

In promotion and advertising, we regulate the manufacturers and the manufacturer that promotes their products. Certainly we have jurisdiction over any distributor -- a second seller of the device -- if they promote a device for an unapproved use, we certainly have jurisdiction over that. If a physician uses a medical device through the practice of medicine, of course, under FDAMA and the practice that FDA has held, I mean, we are not involved in the practice of medicine.

If, however, that physician promotes a device for a use that it has not been cleared for, then the FDA does have jurisdiction. If an individual, however, who is not selling or distributing a device makes certain statements concerning how great a device is, even if it is for a use that it has not been approved for, we have no jurisdiction over that.

So, if you have a device or a drug that you have used and you think it is great and you want to put up an Internet site and you don't hold the product for sale, the FDA really has no jurisdiction over it.

For the Food and Drug Administration, we regulate advertisements, promotional labeling, which would be brochures, pamphlets, any written, printed or graphic material that is distributed by a manufacturer, any statements that a manufacturer may make concerning a new device, press releases -- we have sent letters to companies who have misspoke in a press release concerning the approval of their particular product. We look at the Internet and we look at other activities and other activities could be fairly broad.

A manufacturer supports a particular symposia and in that support of it, they encourage the speakers to talk about the off-label use of their product. We regulate the device and the only reason I bring this up as an example because I think it is important when you look even at genetic testing. We regulate the device and how it is promoted and not necessarily what the device can do.

FDA rarely takes action against the practitioner. For example, you will see ads in any magazine that -- for plastic surgeons, for example, who advertise the fact that they do liposuction. Until a few years ago, there weren't any devices that were really cleared to make promotional claims that they could be used in that particular procedures. The practitioner in making the advertisement that they do liposuction, they weren't advertising a specific device. They were advertising a service that they provided.

Lasik is another example. If an ophthalmologist advertises that they could do Lasik and a few years ago when there were no lasers for that particular use, if the practitioner didn't identify the specific laser, whether it be Summit or Visix, if you didn't identify the laser that was actually being used, FDA really didn't take any action. That is where we depended more on the Federal Trade Commission for the advertising of the service that the physician provided.

Drugs of abuse testing, if a laboratory, for example, says that they do drugs of abuse testing and they don't advertise any specific device kit that they are using, my particular group will not be involved in trying to regulate that advertisement. We have seen ads for Lyme disease, we have seen ads for predicting heart disease and in many cases those ads don't identify

the device itself. There was one case in predicting heart disease where a company was actually advertising a specific -- I think it was an MRI device that was being used to predict heart disease and we sent them a letter.

Eventually, they took out the device that was being used. When we look at advertisements, we make no distinction between professional advertising and direct-to-consumer advertising. For us, we are fairly limited because of the Food, Drug, and Cosmetic Act. It makes no distinction. We have written no regulations that say if you make a direct-to-consumer advertisement targeted specifically for the consumer, that you must include certain information as opposed to if you make an advertisement for a professional.

I mean, if you are in a journal, most of those are professional advertisers. I don't know what the reason for this is, but a lot of the professional ads end up in the doctors' offices and they are sometimes promoted to consumers anyway.

In promotional labeling, which are pamphlets and brochures, et cetera, that companies send out, doctors use in their offices, if it is a 510(k) or a PMA device in any labeling, they have to have what we call relevant warnings, contraindications, precautions, and side effects and the intended use. What "relevant" means in this case is a decision to use the device, whether it is by the professional or by the consumer. So, if it is says it is contraindicated in people with heart disease, that is something that the patient should know so that they can feed in that information to the doctor and that is something the doctor should know in looking at the advertisement.

A lot of people take information from ads, as well as from the labeling in the product. In the advertisements, if it is a restricted device, then under Section 502(r) of the Act, they have to have the same information, the intended use and the relevant warnings, contraindications, precautions, and side effects.

The down side in this is about 90 percent of the devices in the marketplace are cleared through the 510(k) process. Since we don't regulate the advertising for this and we can't

require in an advertisement that warnings, contraindications, precautions, and side effects be included. So, a consumer reading an ad a few years ago or just a short while ago, when breast implants, for example, were under 510(k), they didn't have to have the warnings, contraindications, and precautions.

As soon as they received their PMA, now the ads should have changed where all of that information, which is important to the consumer in making a decision as to whether or not they were going to have that implant.

The Internet, which is another big issue, some problems. The FDA at this time has not issued an Internet policy and because they haven't, we haven't declared the information on the Internet to be either labeling or advertising. We still regulate anything promoted on the Internet for the intended use and the intended use is what the device is actually cleared for.

We have allowed companies who use the internet to have separate sites, both for their international sales, so if you have an icon on the Internet, when you look at the home page for the particular companies, you see an icon that says "U.S." and an icon that says "International." Usually if you click on the international one, you will see the device and how it is sold in other countries for the additional uses that have not been cleared here in the United States.

On the Internet we certainly -- I use the Internet everyday. We use it as part of our job. We see the sale of unapproved devices. Domestically, we see IVD test kits being sold. We see fraudulent devices being sold and in the international market what the Center for Drugs has been doing recently is that if international companies have been trying to attract customers in the U.S. and sell unapproved drugs and there has been a lot of press, for example, on Propeicia, Viagra, et cetera, coming off shore, the Center for Drugs is starting to issue what they call cyber letters, which is using the Internet and sending the letters of warning to the companies in foreign countries.

We also have a lot of cross-border promotion. We looked at one the other day where a Canadian company is selling test kits in the U.S. and also encouraging patients to come to Canada for tests that are not available in the United States.

I have some examples and some of these somebody sent me some examples through the fax in preparation for this presentation. In the area of in vitro diagnostics, we have had a lot of issues with PSA testing, a number of PSA test kits and these are test kits -- we haven't got into anything else yet, but these are kits that are manufactured and sold to physicians' offices or other laboratories for use.

We have had a lot of problems when PSA tests have been cleared for monitoring patients, who have been diagnosed with prostate cancer. The manufacturer turns around and takes this PSA kit and then advertises it as a primary diagnostic tool. That is actually a PMA requirement. So, the problem we have run into is when a manufacturer comes in and gets a 510(k) for a particular IVD test and you will see other examples through here, the thrombos precursor protein test that was approved. I think that was also a 510(k) and that was -- all it did was give certain indicators. If they were present, then the physician looking at the test results could make some prediction as to where the patient was in relation to heart disease.

But the company came out and again promoted the fact that this was a good tool in diagnosing or predicting heart attacks. Aneuvision assay, that was something that someone brought up to me. This is a difficult one. Aneuvision assay, this was a test that was cleared by the agency to be used in conjunction with standard cytogenetic results. The Aneuvision assay, what it was was a rapid test that could give test results for a woman who was pregnant and it would give some indications, because of what it disclosed, whether there was a probability that the fetus could be a candidate for Down's syndrome.

The test, which I think was 510(k) when it was cleared was only to be used in conjunction with standard cytogenetic results. The results on the rapid test came back in 24 hours, but the physician, unless there was some unusual circumstances, was not to tell the patient

what the results were until the cytogenetic results were actually run. Now, the standard cytogenetic test usually took about two weeks to get results. So, the results between the rapid test and the standard test were fairly close. So, what the company started to do was promote it as a stand-alone test, that it could relieve anxiety for the patient, that they could tell them right away. They didn't have to wait for the standard cytogenetic test.

Well, my office sent them a warning letter because that is not what the approval was for. The reason I said this was difficult was because in this case the results of the rapid test were close to the standard test. But, again, this was based on the clearance and based on what they were approved for, we felt that they had gone beyond what they were cleared.

Another one that we had was PSA immunoassay and this was cleared again to detect bladder tumors and diagnose patients, patients that had already been diagnosed and this was to detect bladder tumors as a monitoring test and the off-label claims for this particular immunoassay was, again, as a primary diagnostic tool.

The problem with many of these IVDs that have been cleared is in many cases that is the only thing that is available. So, practitioners or laboratories are starting to use them even though they are only cleared for monitoring as a primary diagnostic tool.

In the area of genetic testing, again, if it is a genetic testing service, if they advertise the service only, FDA probably does not have jurisdiction. So, if there is an advertisement that says we do genetic tests to predict whether or not you are a candidate for breast cancer or you have the gene that you have a higher risk of getting breast cancer, if they only advertise that service, from my point of view, there is probably nothing we could do about it. If they advertise a device test kit that is used in that particular test and it is an off-label advertised use for that particular device, then we would have jurisdiction.

In the home brew testing area, my particular office has had no issues with the home brew area. We usually, because we are not quite sure where those fall, and what I put down here is that if the home brew testing, if they are using ASR, which are restricted devices by

regulation, then if they advertised and took orders by the order of a practitioner, then that would be a violation of the regulations because the restricted device regulations say that for ASRs that the test that takes place had to be on the order of a physician and the results, as we have looked at it, have to go back to the physician.

If they develop a test in house as a home brew and then put a kit together and then sold it to other laboratories or physicians' offices, then the FDA would have jurisdiction and it would be basically an unapproved device that would require clearance before sale.

So, I know you are interested in the home brew area, but I haven't really done a lot in that area. We haven't had a lot of complaints. But I would be happy to answer any questions that you have concerning promotion and advertising.

DR. MC CABE: Questions for Mr. Tart.

DR. BOUGHMAN: I would like to pick up right where you left off and that is the question arose in my mind that when you were talking about individuals versus distributors and whether you would have jurisdiction or not. Because we are dealing with home brew tests at this point, even if they would not be put together as a kit, as we move forward, how do you see or might you talk a little bit about the options for regulatory schemes or for your office oversight for the home brew element or piece of DNA or whatever, even if it is not put together in a kit. Would you see that potentially being redefined or better defined to fall into a distributor category and, therefore, under your jurisdiction?

MR. TART: Well, when I said it is under our jurisdiction, what I meant was that the laboratory is a distributor only in the context that they are offering -- they are not really offering a device. In other words, they are offering a service. We wouldn't really have any jurisdiction from my standpoint anyway over promoting the particular service.

DR. BOUGHMAN: Rather than doing the tests themselves, if they were providing this portion of routine DNA testing to other laboratories so that they might perform the test --

MR. TART: Oh, then that would be -- yes, sure. Then FDA would have – they would then be selling the device to someone else.

DR. BOUGHMAN: Even if it is not put together with ASRs in a kit. You haven't been present at a lot of our conversations, but one of the things that I have been really impressed by this Committee is trying to get our hands on from a variety of perspectives, what already falls into schemes and regulatory mechanisms and how, rather than reinventing regulatory mechanisms or adding new ones, how we might, in fact, inform that process, given the explosion of genetics research and activity. I think we have hit on this last piece in one of those potentially critical areas.

DR. GUTMAN: Yes, I actually think -- probably Byron can't answer that because you are looking at something incremental that is unexplored at this point, a potential desired outcome would be to have heightened ability to police claims in this particular area since that is actually essential concern is what is the clinical validity and what is known and not known about a test and again whether we can pull it off or not, I don't know. But a desirable thing is if you start claiming that something not known about the test is claimed and you advertise it, I hope at some point in time, Byron can go after them.

DR. KOENIG: I just wanted to follow up about the issue of your regulation of ads or promotional material -- I guess it would have to be ads in this case, that don't mention a specific product. Is that comparable in what in pharmaceuticals is called non-branded ads? I mean, where you promote a kind of drug basically but you don't ever mention the name of it?

MR. TART: Well, I think it is a little different. I think what the physician is doing is advertising the intended use basically. I mean, they are advertising a service they provide as opposed to saying, we use the Visix and Summit laser because they are great to do Lasik. Now, that is approved now but it wasn't a few years ago.

Now, if the physician only says it is part of our service, we fit contact lenses, we do eyeglasses and we do Lasik, and that was just listed in that, even if there was no device

approved for that particular use, the device itself is not being advertised. If a laboratory, for example, says we do genetic testing to predict whether or not you have a hereditary gene present for a particular disease, they wouldn't be advertising what they use to do that.

Now, they may be using a test kit that is already available.

DR. KOENIG: It seems to me that if there is only one product on the market that does X, that just not putting X in the ad is -- that this is a huge loophole. Am I missing something here?

MR. TART: That is right. It is a huge loophole and it is basically what we see as service advertising.

DR. CHARACHE: I think this is the same question but am I understanding correctly that if a manufacturer advertises an off-label use, you could get into that?

MR. TART: Even if he doesn't identify the device.

DR. CHARACHE: Right. But if a laboratory advertises that they can provide an off-label service, is there any group that can get into it?

MR. TART: Well, I mean, this may be where we are between the Federal Trade Commission and the Food and Drug Administration. If a manufacturer, for example, says we have devices that do Lasik but don't identify the device, we would still hold the manufacturer responsible because they have got the clearance for the device. They are known for that device, et cetera.

In the case of a laboratory, if -- I don't know what the laboratories use. I mean, they could be using a kit that has been approved already by FDA. They could be using it off-label extending the use of that particular kit. From an advertising standpoint, when we write a letter to a company, we have to established jurisdiction and by establishing jurisdiction, we would have to say such and such is a device within the Food, Drug, and Cosmetic Act as defined by the Food, Drug and Cosmetic Act.

The service is not, whether they do Lasik or PRK or genetic tests, that doesn't necessarily give us jurisdiction even if there is only one device out there that could or could not do it.

DR. MC CABE: Steve, I will give you the final comment because it sounds like we are getting into a discussion that would be better to have with Mr. Daynard at the table also.

DR. GUTMAN: Okay. Well, I don't want to make false promises, but when the lab becomes a manufacturer, which is a possible outcome of the new regulatory scheme, then the rules potentially could change. So, there is a possibility for stronger enforcement in the future.

MR. TART: If the lab becomes a manufacturer, then the same rules apply as they would to any manufacturer.

DR. GUTMAN: But you never get over the off-label use issue that was at the table. An iconoclastic physician right now can order sodium to diagnose brain cancer if they want.

DR. KOENIG: One really quick comment or question that is just factual. What about educational materials that you make a distinction between professional and direct-to-consumer ads, but what about educational videos that you call up and get through an 800 number --

MR. TART: From the manufacturer? No, no, we don't call that educational. We call that promotional labeling. It is regulated.

DR. MC CABE: Thank you very much, Mr. Tart.

Mr. Daynard will speak to us next. He is a senior attorney -- Mr. Tart, there is a place at the table for you if you want to -- or if you want to sit around here, we can move your name tag around to make it more comfortable for you -- Mr. Daynard is senior attorney for the Advertising Practices Division in the Bureau of Consumer Protection at the Federal Trade Commission. During his 29-year career at the FTC, he has helped direct many of the

Commission's major law enforcement and consumer education activities that address fraud and deception in the delivery of health care services.

He has appeared here before, works together with many national and state bodies regarding health care issues. Mr. Daynard received his law degree from Columbia University, is a member of the bar in New York and the District of Columbia.

I also want to mention that Mr. Daynard attended our public consultation meeting in January. Thank you for coming, Mr. Daynard, and welcome back.

MR. DAYNARD: My pleasure. Thanks very much to the Committee for inviting me. If I had answered your question earlier, we probably could have in the interest of time skipped my presentation. So, perhaps I will just answer it now.

I want to give you a quick, really basic overview in 20 minutes of these topics; our jurisdiction, who we are and what we have jurisdiction over, how we look at advertising and what we tell marketers in order to comply with the Federal Trade Commission Act, what we have done in the area of privacy. It is a very hot issue as you have seen in the newspapers and I assume it is going to be a hot issue with genetic testing. It has always been, as far as I know.

We have been heavily involved in it. We have had some cases, recommended legislation to Congress and involved with the industry. So, I will go over a couple of those things.

We have a project we call CureAll, which involves Internet advertising for safety and efficacy claims, for prevention, cure or treatment of serious diseases. We have done a service with many other countries, with AG's offices and other folks and we have found it is a wild, wild west out there. We have jurisdiction over the Internet. We have brought cases in the area.

We have sent teaser sites up on the net where we have ArthritiCure and we tell the consumers it is going to cure their arthritis and as they click on by it, it goes "Gotcha" and says if this had been a real site, you would have wasted your money. The HIV home test kits,

cases we have had in that area are probably the closest analogy I can find that we have been involved in to date for genetic testing. So, I will talk about those a bit.

And industry and consumer education, believe it or not, is a big part, perhaps even an equal part now in what the FTC does because we believe that prevention is the best offense.

Here is our jurisdiction. It is very broad. Unfair and deceptive acts of practices in and affecting commerce are prohibited. There are no distinctions for on-label, off-label or anything else in general, other than C3 non-profits, I guess. Also we have jurisdiction of false advertisements as sort of an extra added attraction that Congress gave us to add to our complaints if we want to or to bring a preliminary injunction in certain cases over foods, drugs, devices and they added services just a few years ago.

It is funny, it took a bookworm at the Commission, namely, me, a couple of years ago -- I don't know why I was doing this -- I am not normally a bookworm -- to find that they had added to this definition of false advertisement, services. But there is no definition of services as there is for foods, drugs and cosmetics and devices. So, we figure -- they are talking about health services, of course.

Now, this jurisdiction includes any ad claims by any marketer of any genetic test, including off-label uses. There is no distinction whatsoever. Our jurisdiction covers all persons, partnerships, and corporations. So, it is very broad.

The answer to your question would be that the FTC could get involved.

Here is the definition of "deception." Perhaps you don't need to see it. It is in your syllabus. Representation in mission or practice is deceptive. It is likely to mislead consumers acting reasonably in the circumstances and of material; that is, it is likely to affect their choice or their conduct or their use of a product or the decision with respect to the product or service.

The nice thing about this definition is we don't need to show intent. We don't need to show harm. If there is a likelihood to deceive, it is within our jurisdiction and we can bring either a civil action between a civil action federal district court or administratively.

We have another prong and that is unfairness and this was codified into our statute just recently by Congress. A practice is unfair if the injury to consumers it causes or is likely to cause is, one, substantial; two, is not outweighed by countervailing benefits to consumers or to competition, sort of a public policy prong, and, three, is not reasonably avoidable by consumers themselves.

The nice thing about this is we don't really even need an advertisement. Something can be unfair or unconscionable just, for example, if there is some know risk associated with, let's say, a prescription drug. You all remember the Phen-Phen fiasco awhile back. Well, we were all ready to bring cases on the theory of that just by advertising Phen-Phen by retail by physicians. It was unfair because it was known at the time that it was associated with heart valve problems and wasn't disclosed to consumers. So, we could bring a case -- the FDA bailed everybody out of that one or I guess the company did. They asked the company to withdraw the drugs and they did.

So, unfairness is another prong that we use. It is rare that we use it because it is difficult to meet all those prongs, but it can be used and prescription drugs or drugs in general might be a good area or even genetic testing. Here is the agreement that Byron alluded to. What it means is that we have an understanding and the understanding is that the FTC has primary jurisdiction for the advertising of devices among other products and the FDA's primary jurisdiction for the labeling of those devices.

What it means is that if there is an advertisement for a device that comes to my attention, I will call up Byron and I will say, listen, here is an advertisement. What do you want to do. Maybe it is labeling. Maybe it is advertising also, a promotion that I would deal with and we coordinate it because we can have dual jurisdiction in many instances and we want to

coordinate our efforts. We have often done things together at the FDA and the FTC or if we are too busy or they are too busy -- but it is important to know that there is this general distinction that FDA takes care of manufacturer labeling and we take care of advertising.

Here is what is important to the FTC. True and substantiated safety and efficacy claims for the prevention and treatment or cure of serious diseases are an important part of our mission and we have substantial resources in what is a very small budget devoted to that. Why are we interested? For the obvious reason that injury to consumers can be serious should they use the wrong product or service or if they forego beneficial treatment. Otherwise, beneficial treatment has been proven to be so.

It is also important to know, though, that we don't regulate how doctors use or prescribe drugs or devices or services in treating patients or in choice of therapy issues. So, once a consumer is a patient, we generally won't get involved in what the doctor says to that patient. It has happened in a very unusual case involving infertility treatment, where the doctor in Virginia was telling women that they were pregnant when, in fact, they weren't and then he was telling them that the fetus had resorbed, whatever that means, into the interior wall.

So, we settled in federal district court and we got a quarter of a million dollar judgment and then the U.S. Attorney's Office got involved and the Virginia State Medical Board. They found out he was using his own sperm in the infertility treatments. This guy is in jail. But it is very rare that we will get involved in the doctor/patient relationship, once that relationship comes to bear, but we will get involved and the advertising physician does before that time.

Here is what we tell marketers. It is really very simple. There is a much longer version, by the way, of all of this in your syllabus. In the interest of time, I didn't want to go through it all. What I tell them is tell the truth. Don't mislead consumers about the benefits of safety or your products or service by what you say expressly or even impliedly. Tell all the truth. Don't omit information that is necessary to prevent deception and make sure it is the truth. Make sure you have competent, reliable evidence and support for your claims.

Here is another way of saying it. Advertisers are responsible for all their expressed and implied claims. It doesn't have to be an expressed claim, that genetic testing is going to diagnose an illness or predict heart disease. It could be implied. What can it be implied by? The net impression of the advertisement. We look at everything, before and after pictures, the text, the product names, any other visual images. If it is on the web, some hyperlinks that might be involved. Even meditags, hidden messages that might be included in Internet web sites that we will look at that might even have imbedded messages in them.

We have, in fact, an Internet lab at the FTC where we try and stay on top of the gimmicks that are used by web site developers and believe me, they are quick and they are fast and we tend to be on top of it.

This is a key to how we look at advertising. All marketers have to have substantiation for their claims before they disseminate the ad. The standard is flexible. It is not necessarily the gold standard of placebo-controlled, double-blinded, randomized studies. Those would be the best, but it is not necessarily what we require. It is flexible because it depends on the claim. Every case is different for the Federal Trade Commission. It is all ad hoc. We look at how the claim is presented. We want to make sure the consumers have access to accurate information even for emerging sciences or devices or products or services, but at the same time it has got to be competent, reliable, scientific evidence.

How we determine that, since we are not scientists, we call up the experts. We call up the experts both in the field that the ad might pertain to, cardiovascular area, for example, and if it is an herbal or a botanical, we might call up someone who has an integrated medical practice, who deals with that herbal or botanical or who is a researcher.

Testimonials are our big issue. I am not sure what role they will play in genetic testing advertising, if anything. It may, but the important point here is that marketers can't say indirectly through a testimonial what they couldn't say directly. You can't use a testimonial to make the underlying claim and the Commission requires just that. If there is a testimonial saying

I lost 30 pounds, one, that is a claim that this product produces significant weight loss and, second, it is a claim that it is a typical result. Consumers who use this product or service will lose significant amounts of weight.

If that is not the case, then the advertiser has to disclose what the generally perceived result will be or the consumer should not expect to get that result.

The results may vary. What you probably see all the time is not an adequate disclaimer. Consumers could actually do better under that theory. Third party literature is important to the FTC; one, because of the first amendment and we won't challenge content or accuracy of books or articles or non-commercial literature. On the other hand, the FTC does prohibit the deceptive use of third party literature. What does that mean?

Well, the bottom line really is that the primary purpose of using the literature is to propose a commercial transaction, i.e., the sale of a product or service, the FTC probably has jurisdiction. It could be a murky area. We have gotten into some spats with the tobacco industry over this. But generally -- I mean, this is what I tell marketers to avoid. If they are going to use literature, if they are doing to have literature in their offices for consumers to see, they had better make sure that claims made in those brochures have some competent, reliable, scientific evidence to back them up.

Here is what we have done in privacy. It is way too long to go into, but we have been involved since 1995. We have had public workshops. We have done surveys of commercial web sites with annual reports to Congress for the last three years. The Federal Trade Commission itself endorses the widely accepted fair information practice principles of notice, of what your information practice principles are, giving consumers choice as to whether the information they are going to provide can be used in certain ways, access that consumers can have to their information that they do provide wrong information and security to make sure that it is not used or misused by unauthorized persons.

We have also engaged in law enforcement actions and we engage in education of consumers and businesses on privacy on an ongoing basis. I just saw something the other day about privacy in genetic testing that I thought would be useful; 92 percent of consumers in a recent survey even oppose the idea of using their genetic information for research without prior consent from a Gallup Survey in August. So, privacy, as you all know very well, is going to be a big issue here.

Here are a couple of cases -- it is in your syllabus -- that we have been involved with in privacy. We settled charges with GeoCities, which is now a Yahoo subsidiary, that the web site had misrepresented the purposes for which it was collecting personal identifiable information from kids and adults and Liberty Financial Companies. We challenged allegedly false representations on a young investor site, that information collected from kids in an on-line survey would be maintained anonymously and in fact that wasn't the case.

We have also challenged what was really a fraudulent on-line privacy. They purported to be a network of pharmacies with an actual clinic. Actually, they had one doctor in a distant state, who for ten bucks would look at applications from consumers and they charged consumers 75 bucks for the consultation. They represented all sorts of nice privacy protections to consumers, none of which were true. It wasn't a network. It was just your local drugstore that was filling the prescriptions.

These are the orders that we got here. One order prohibited all those representations and required the defendant to establish and maintain reasonable procedures to protect the confidentiality, security, and integrity of consumers' personal information, to provide reasonable means so that the consumer may access and review their information, and to provide reasonable means by which a consumer may modify inaccurate personal information; basically, the fair information practice principles.

It also required that they post a privacy notice that they were going to do business in the future that will contain those information practice principles. This is in your

syllabus. These are good resources for what the Commission is doing in the privacy area, all sites on our web site.

We have been involved -- here we have coordinated with the FDA. These were unapproved HIV home test kits. We challenged the defendant's representation in the federal district court that their HIV home test kits accurately detected HIV. We had them tested. It wasn't true. The order bans the defendants for life from marketing any HIV home test kits. The defendants have to pay back the money they received from the sale of those kits and if they get involved in the future in selling any medical devices, they have to post a $500,000 bond. It is a good deterrent in many cases.

What we also do is have an extensive web site, not as extensive as the FDA's, I suppose -- perhaps if we had more budget we would -- but we engage in extensive industry and consumer education on a continuing basis. In fact, when we have any case that is going to federal district court or even administratively a component of our recommendation to the bureau director is what is going to be the educational piece that is going to go along with it.

What we do for industry is we have got advertising guidelines on our web site. The first one there is all about the Internet. Yes, marketers, you are responsible for what you say on the Internet. It is not the wild, wild, West. The FTC Act does apply and online rules of the road tells them how it applies. The second two -- you actually might want to take a look at the dietary supplements one. It is really an excellent exposition of how we apply FTC law and gives really good examples in the dietary supplement area, but it is applicable to any area, including genetic testing.

For consumers, we have facts for consumers listed both on our web site and available through the Consumer Information Center in Colorado and they cover things like diet, health, and fitness. We have one on home use tests for HIV and we consider those very important.

For any of you who are interested, this is in your syllabus, if you want to talk about any of this beyond this meeting, there is my name, phone number, and e-mail address. I am happy to act as your hotline at the FTC now and in the future and I am happy to take questions.

Thank you very much.

DR. MC CABE: Thank you very much.

Are there questions specifically for Mr. Daynard before we open the conversation with both of these gentlemen?

DR. TUCKSON: Regarding the Internet material, I don't know whether you are aware of the study done recently by the California Health Care Foundation on Internet privacy.

MR. DAYNARD: Yes, I am.

DR. TUCKSON: Did you find that helpful and did it sort of ring true?

MR. DAYNARD: Well, it was --

DR. TUCKSON: Can you maybe help the rest of us?

MR. DAYNARD: If we are talking about the same thing, the California Health Care Foundation came out with a report in February or January that looked at 21 health-related web sites that provided information to consumers, ask Dr. Udell and take a health assessment survey to see what your risks are. They have privacy policies and what the report did was look at whether those privacy practices matched their policies. If a policy says we are not going to give any of your personal information to third parties and then they do, either inadvertently or through some source code or HML code or Java Strips or something imbedded in their web site, then he had this little alarm clock that he showed and there were problems.

There were some serious problems where either disclosures to third parties or agents -- interesting issue, who is a third party who might do something with your data and who is an agent under contract, but that is another story -- but he did show that there were several problems with either inadvertent disclosure through these methods of transference of code back

to web servers and he showed there were some intentional or seemingly intentional transference of personal information or even non-personal information to third parties about the use of banner ads by such advertisers as Double Click might collect information unbeknownst to consumers.

So, it was a really good thing and it was nice of him. He notified all those companies in advance and saying here are some problems. What are you going to do about it? We instituted some investigations, just between you and me for the moment, and so some of them have stopped. Some of them we are still trying to pursue.

I mean, they all were flabbergasted that they actually had to comply with something that is required under the FTC Act or even public policy or the right to privacy, but I have to say in their defense so far that they are doing a pretty good job of correcting problems.

DR. MC CABE: Other questions?

DR. KOENIG: Can you specify the nature of your review in terms of the timing, of publication of an ad? Is there any category of these things, whether they are on the Internet or education, that you would actually approve before they are made public, so to speak?

MR. DAYNARD: There is only one circumstance -- we don't engage in censorship. But we do have what is called advisory opinions, both informal and formal. If a marketer wants to -- in effect, what I tell marketers is if you have an advertising about Lasik, for example, where I am involved, that you want to market and you are not sure about it, give me a call. Tell me what you want to say and assuming I know the science, which I generally do in Lasik, I could give you an answer.

There is a formal method where one can go to the Federal Trade Commission. It takes a long time and folks don't generally want to do that. It can happen, but once the ad is published. – no. Now the other thing that happen once an ad is published is if there are lots of local advertising going on, like with Lasik, the Federal Trade Commission is not going to sue 10,000 marketers of Lasik -- it doesn't have the resources and doesn't want to run rough shod

over state laws, which all have the same FTC Acts basically. So, that is probably not going to happen.

So, what we might do, though, is send an advisory letter to a marketer, saying, well, here is the American Academy of Ophthalmology guidelines. Here are the FTC guidelines. We are not saying you are bothering the FTC Act, but you may want to reconsider. They will give me a call. We will talk about their advertisement. Assuming I know the science, again, they will fix it generally.

So, we can do that, too.

DR. MC CABE: One last question from Pat Charache and then we will move on to the open -- the broader discussion.

DR. CHARACHE: This is returning to my earlier question about the ability of the FTC to address a service. I am thinking -- you may already know about the man who is the only one in the world who can detect a stealth virus, which is advertised very extensively on the Internet, that if you send your sample to his laboratory, he will diagnose the stealth virus, which will explain chronic fatigue syndrome, rheumatoid arthritis, and a few other things.

Now, would that be covered by the FTC?

MR. DAYNARD: The ad is covered, certainly.

DR. CHARACHE: The web site statement?

MR. DAYNARD: Absolutely.

DR. MC CABE: Why don't you join us at the table, please, Mr. Daynard, and we will open this to a broader discussion with both Mr. Tart and Mr. Daynard.

While Mr. Daynard is taking his seat, I just draw your attention to something that Judy Yost and her group put together for us that is in your green folder on state genetic privacy laws. Oh, I am sorry. It is a different thing. It is the identified state requirements that were prepared by Judy Yost's office that has to do with oversight in general and the issue of direct-to-consumer marketing and points out that many states have jurisdiction over licensure -- well, all

do over licensure of health professions. Most have policies outlining who is authorized to order and receive test results.

So this can help us with both explicitly allowing patients to order tests. A few of them allow patients to receive the test results. A fair number of states have no defined requirements in the area. So, that may be quite helpful for people to look at.

So, let's open up this discussion now.

Discussion

Remember, the etiology of this was a concern about direct-to-consumer marketing of genetic tests.

You have changed hats, Reed, recently and I am wondering if you would have any thoughts from wearing either of those hats?

DR. TUCKSON: From both perspectives and naively at the newest one, for a day, so the hat, I am not sure, is going to fit yet, I will say there is real concerns about the manipulation of the public and I think that also there is a real concern that -- the other Oprah had a guest on her show that -- and she actually went through a total body scan, where basically you go from head to toe and you get this wonderful intimate look at every thing in you.

So, subtle abnormalities, small clogging of an artery, a weakness, perhaps, a beginning of an aneurism maybe. Everything sort of pops up. The demand curve for this kind of thing is going to be very high. Now, what the hell do you do with it when you get these results and who in the world is going to be able to pay for it? Rich folks maybe can get it done.

But it is that kind of thing where now we can certainly expect I think with direct-to-consumer, again, just somebody pushing this. So, I guess at the end of the day are you, in terms of the bulk of the presentations here, what is your ultimate answer back to us in terms of what more is needed or what should we be suggesting to give more protection, such that people are not caused to ask for things that they don't need, that they are not going to be running into

doctors' offices demanding stuff, that poor doc is not going to get overrun by somebody asking for yet another antibiotic to treat that cold and so forth?

I mean, is there any more at the end of the day that we need to recommend than what you have available in your armamentarium today?

MR. DAYNARD: This is probably more an FDA question than FTC, but I can tell you right now we are not going after Oprah. She is too big.

There really isn't much to say about the Federal Trade Commission Act. I mean, you saw in my presentation that our jurisdiction is broad and really unlimited with respect to advertising. So, if there is any advertisement you can think of regardless of what it says, it is subject to the Federal Trade Commission Act, but, again, it is a case-by-case basis. I mean, if there is just an ad saying you can get this test done that looks in your entire body, there is no problem with the FTC Act if it can do that.

So, you are asking a different question in that sense. The FDA may have more.

DR. MC CABE: Wylie, you had a comment. Then Susanne is going to show you some phony ads that were made up and have you react to some of those, if you would.

DR. BURKE: Actually, my comment is I am sure it occurs to many of us that there is a culture -- we live within a culture that tends to assume that knowledge is good and one of the tricky things about the risks of genetic tests is that they include getting information that actually may do you harm just intrinsically as information.

I guess if I am hearing correctly, an ad that proposes that a certain kind of information from a genetic test is a good idea and it provides that information would not be out compliance, even if there were tremendous concerns about the personal or social risks of having that information.

MR. TART: I know awhile back we saw a number of ads for a company called HeartScan and there was even one in Washington, D.C. and I think there were a number of centers throughout the United States. Their advertisement said, come in, get scanned and we will

be able to tell you whether or not you are a candidate for a heart attack. Now, there was really no evidence that -- they could show certain things and the device had been cleared for that.

I didn't mean to say that FDA couldn't do anything. When we see a particular advertisement, even though my particular office may not have jurisdiction because the device itself is not being advertised. It doesn't mean that FDA couldn't send out an inspection to go to the laboratory, for example, to see what components were used in the kit, to see whether or not they were using an approved test, off-label, or whether or not they were making up a home brew.

If it was a home brew and they were using ASRs and they weren't getting on or by the order of a physician. So one of the elements may be that if a company or laboratory who advertises a service piques the interest of the Food and Drug Administration and an inspection results because of their particular advertisements, this may make them more cautious in their ads, but with the Internet with -- there are a lot of ads and promises out there that FDA has little or no jurisdiction also.

DR. TUCKSON: Let me make sure again to my question, just to push you very hard. I mean, you are a Federal Government official and you have got your rules. I just want to know what you can and cannot say.

At the end of the day when you boil all this down, final analysis, your grandmother, your daughter, what, if anything, is needed for this Committee to recommend to the Secretary and I know I am being deliberately mean and pushy, so that if you get in trouble, you can blame me.

But is there anything that we need to attend to in your opinion that is not -- or is everything okay, let it go? It is running fine. Don't fix it. If it ain't broke, don't fix it.

MR. TART: It is not broken and I don't really have an answer for you as to what we need at the end of the day so we could increase our enforcement over, for example, I guess you are saying advertisements which don't identify the particular device. The Act would have to be changed. I mean, the Food, Drug and Cosmetic Act would have to be changed. I mean, I

think FDA has taken upon itself to provide education to consumers. They have gone out of their way, especially even in the device area to provide information, for example, in breast implants, when they didn't have real jurisdiction over some of the advertising to advise the consumer.

I am not sure how to answer what we need. I mean, the Act itself is pretty explicit.

DR. TUCKSON: Thank you.

DR. KOENIG: I just wanted to put the discussion -- to frame it in a broader social context, which I think is going to be relevant to our discussion tomorrow about informed consent and that is that we are moving, I think, socially into an era in which more and more decision-making authority is going to be at the level of the individual consumer. Since we keep coming back to the issue the important things are disclosure of what we know and what we don't know, then I think this issue of how this information gets out there is important.

I just want to provide a couple of statistics as disclosure myself. I actually have a small grant from the Greenwald Foundation to look at some issues of direct-to-consumer marketing of pharmaceuticals and how that -- as a bioethics issue in terms of some of the ways in which it affects how people make choices.

This was prepared by my colleague working on that project, Linda Hogel. She said, "The pharmaceutical industry spent 13.9 billion on all promotional spending in the U.S. in 1999, an 11 percent increase over 1998. This includes professional detailing, samples, advertising, and promotion. The proportion spent on direct-to-consumer advertising has increased steadily. It has grown from 4 million in 1990 to an estimated 1.8 billion in 1999, with an increase of 40 percent over 1998. The proportion spent for television increase, 70 percent, to 1.1 billion."

So, this represents a major shift in promotional spending for drugs. I won't go on. I have got more information if anyone is interested, but I think that sort of presages what will

likely happen with devices. I think we need to be thinking about this. This is sort of a major strategy change, it seems to me, partly brought about by changes in the law, about what was allowed.

MR. TART: I think one change that could be made at the end of the day, which the agency has tried for some time is that if -- the 510(k) devices, which are advertised to consumers, which we don't have jurisdiction over -- the agency has tried for a number of years to get through what they call a restricted device regulation, which would reclassify or set standards to fit the 510(k) devices into what we would call restricted devices.

That certainly would give the agency jurisdiction over the advertising, would require manufacturers to put in the warnings, contraindications, precautions, which is relevant information to consumers considering the use of these devices. This is what we don't have now.

DR. MC CABE: Thank you.

MR. HILLBACK: I would just like to make a comment just to get closure because I think while the statistics are interesting, Barbara, you do make the point that you are going from a period where it was illegal to do this to a period where it was legal and it is like saying that is a hundred percent growth from we didn't have this. So, I think we have to be a little careful.

I am not an apologist for people doing bad advertising at all but we have to be a little careful about how we throw numbers around.

DR. KOENIG: Well, but I think the fact that the law changed is part of the whole context. I mean, it changed because of this fundamental change in who should be responsible.

DR. MC CABE: I think it also is a fundamental cultural change. It is not just a legal change. People are taking responsibility for their health, where they used to delegate that to a third party, to another individual. So, I think that we are going to see people being educated about their health, using the Internet for that as well as other media.

We, the people, are demanding this, some decision-making about ourselves. But it does mean that more individuals are going to be accessing this sort of information.

Susanne, let's see some of your creativity, if you would, please?

DR. HAGA: I don't work for an advertising firm, but there were two articles that caught my eye when we were planning for this meeting. One came out of the U.K. on some research that they had done connecting genes and smoking and what they found was if you figure out what your metabolism is from nicotine, you can better choose your antismoking therapy. The patches may work on some people but drugs may be more appropriate for other people according to your metabolism. So, I just ginned up an ad that I thought I might see in a magazine or something for this kind of test.

DR. MC CABE: If our two experts could comment on it. We have granted Susanne immunity.

MR. DAYNARD: I don't know the science here, obviously, but every statement you see there that is an objective, verifiable claim, such that the simple test, designed accurately predict which smokers will benefit, the fact that it is designed to accurately predict is not a shield from the underlying claim, which is that this test will predict it.

The other statement said that it will revolutionize the success rate. That is a claim that it will increase the success rate for antismoking therapies and I am sure there are others in there but the point is that everyone of these objective claims would need to have competent, reliable, scientific evidence to support it or it would be deemed deceptive.

DR. MC CABE: And that would be at FTC or FDA?

MR. DAYNARD: Well, I know it would be FTC. I can't answer the question about FDA.

DR. MC CABE: Mr. Tart, I saw you pointing your finger at the FTC.

MR. TART: Well, a smoking thing is rather interesting because if this was to say, if this promised that you would improve your health, it would prevent heart disease if you

quit smoking and that this test somehow aided you in stopping smoking, it would probably be classified as a device and be regulated as such.

The SmokeGen™, if it is an actual test, it is either -- if this is a manufacturer's ad, then that would be a test that would have to be cleared by the Food and Drug Administration. As the ad reads now, it might be questionable as to whether or not it is a medical device at all.

DR. MC CABE: Thank you.

Susanne, you have one more, I understand. I think this is helpful to me, at least, I hope to the others to see the specifics.

DR. HAGA: Again, this is based on some research done by a lab -- a research place in this country about using markers for colon cancer and how it looked like from preliminary studies that this would be vastly improved from other tests that are used to detect colon cancer at this moment.

MR. DAYNARD: This one is loaded with claims that would need to be substantiated by competent, reliable, scientific evidence. The first sentence might be viewed by some reasonable people as a claim that it is going to prevent colon cancer period. And anyone that doesn't have it now. The next, of course, does it detect over 90 percent of early cancers. There is a comparative claim that it is twice as accurate as the fecal occult test and sigmoidoscopy. Then there is the pejorative comparison down there. Again, it is all subject to the same standards. We would ask the same questions.

DR. MC CABE: This would be FTC. Would this be considered a device then, Mr. Tart?

MR. TART: Yes.

DR. MC CABE: So this would be considered a device as well since it is making claims about testing.

MR. TART: Yes. In looking at how this advertisement is written up, it appears that it is some type of test kit that has been developed to predict colon cancer. Probably be a

device, whether it is a PMA or a 510(k), depending on what the claims would be a decision that ODE would make.

DR. MC CABE: It was done as a home brew, so it is really being done under this trade name, but it is a service. Does that make a difference?

MR. TART: Probably. I mean, if it was a home brew and they were advertising that said see your physician. The physician collects a sample of blood, sends it to this particular laboratory and it runs the test, we would probably look at it more as a service advertisement and then talk with the Federal Trade Commission.

DR. BOUGHMAN: I would like to make the discussion a little broader for a moment if I could. We are clearly moving very quickly in the post-genomic era, if you will, from a medical model where we have been in the business primarily of diagnosing disease, moving to predicting a variety of adverse outcomes that might allow intervention strategies or for preventive strategies to the analysis, the recognition of, the delineation of the genetics of a wide variety of traits in general.

I am wondering in the concept of the Food and Drug Administration, since we are dealing with the Food, Drug and Cosmetic Act if, in fact, there is any challenge in that spectrum. We have been dealing with a concept of disease condition, trait, variety of things and I am wondering if that continuum is, indeed, a continuum or if the FDA or FTC have any limitations on jurisdiction there.

Secondly, another major shift at least in my thinking about this is, in fact, the one that was brought out by the previous ad and that is the concept that genetic testing be linked in the future with therapeutic efficacy and what that might do in the FDA review process and the concept of off-label use, how a company who is putting forward a therapy might include a genetic screening test to make claims on therapeutic efficacy versus our wonderful world of being unencumbered by that information at this point.

DR. MC CABE: Any comments?

DR. GUTMAN: It is a hard question, especially the first part, but as I understand it, when we look at a diagnostic, it is not only for disease, it is for conditions. So, it would depend on how far you would be willing to push condition in terms of some parameter of health status and where you might slip beyond disease or condition.

In terms of selecting drugs, there are lots of diagnostics used to select drugs and I would argue that a genetic test used to select a drug would be a diagnostic if you use it to pick a diuretic instead of an ace inhibitor to treat hypertension. In my mind, that is a diagnostic.

DR. MC CABE: Any comment from our guests?

MR. DAYNARD: Just to answer the direct questions you posed. No, there is no limitation where you switch over from a diagnosis paradigm to a prevention paradigm. Those HIV home test kits were sort of, if you will, a prevention claim for getting AIDS if you know you have got HIV and there was no problem there. I don't see any problem for the Federal Trade Commission. The question is always as a commission what is the claim. Everything they do is claim driven.

DR. KOENIG: Just one quick question?

DR. MC CABE: Well, very quick because we have got these electronic poltergeists.

DR. KOENIG: What would either of your agencies do with an ad for a prenatal test that allowed someone to predict whether a fetus had blue eyes?

MR. DAYNARD: Again, the Federal Trade Commission's hook is the advertising. So, if the advertisement says this test can tell you whether your beautiful child is going to have brown eyes or blue eyes and that fit into our current mission, we would ask them for competent, reliable, scientific evidence that it would do just that. If it wouldn't, we would correct the matter.

DR. MC CABE: Thank you.

We are going to take a break. We will reconvene at quarter of. So, a ten-minute break. Thank you. We really appreciate you coming in. It was very educational.

[Brief recess.]

DR. MC CABE: Let's get started again.

It is time now for Dr. Joann Boughman's report on the Education Working Group's progress and their plans, their next steps.

Report from the SACGT Education Working Group

DR. BOUGHMAN: Thank you.

I have up here the list of our work group and there are several things that we included in your binders and there were some handouts today, including some of the essential points that you will see on some of the overheads.

The committee is not very large at this point and we have only had one official conference call meeting, but there have been, I believe, a lot of various activities that have been occurring, not the least of which and, in fact, quite impressively, Susanne Haga's efforts on behalf of this work group to initiate a search for some of the kinds of educational activities and what is going on in several groups that I will mention.

When Susanne started gathering these data for the work group, we gave them just the tables of contents of the four volumes, each one about 2 1/2 inches thick that she sent to me. That was the first week and a half worth of work. That actually will continue to be an underlying theme that we will present. I would like to thank the members of the work group.

The charge that we had from our gathering in August was to, in fact, get some grasp on the current status of work force analyses. I will turn to Michele Puryear a little bit later to make a comment because, in fact, her agency has been supervising this.

Information gathering about current content guidelines in education in genetics, additional information on groups or activities, including professional organizations and industry,

and specific issues regarding education of genetic professionals, patients, consumers, general population and all others as appropriate, which includes just about everybody.

It didn't take us long to reaffirm the concept that there is a lot going on. There are a lot of highly qualified people and groups out there that are, in fact, putting together curricula, symposia, content guidelines and so on and that the role of the SACGT and initially the work group would be, in fact, to frame the issues or questions to guide our discussions and keep them focused on what the SACGT might actually recommend or do, given that we are not going to, in fact, participate or perform these educational activities.

If you remember, as has been discussed before, each one of our groups was to address the direct-to-consumer marketing issues. We have not focused on that, but I think that the session we just had and others are beginning to frame that discussion more clearly.

Joe McInerney, who has since August been named the new executive director of NCHPEG, the National Coalition of Health Professional Education in Genetics -- Joe is a member of our work group and in a succinct way helped us focus our guiding principle and I think everybody on the conference call was pleased that, in fact, we are here to promote a partnership between providers and consumers, so that genetic testing can be used effectively, even while the knowledge is so rapidly expanding. I think that captures many of the elements of the principles on which the Secretary's Committee has been functioning, but also addresses the challenge we have in this rapidly expanding time.

The collection of materials has been initiated from professional groups and organizations and you have some of those in your binders and you also have a list of some of the many web sites that include a great deal of information. This is only the beginning and we will come back to that issue later.

We have also tried to begin collecting materials on medical and genetics curricula. To this end, I will jump down to the fact that we have been represented at a variety of meetings, since our August meeting. Judy Lewis was at a national meeting in nursing and, in

fact, made sure that they knew that the Secretary's Committee was interested in the genetics curricula and educational activities.

I attended the Information and Education Committee meeting of the American Society of Human Genetics and the Education Committee of the American College of Medical Genetics at the national meetings in Philadelphia to make sure that the members of those education committees realized that the Secretary's Committee has, in fact, determined genetics education to be an extremely important issue and that we will be looking to those professional organizations and others for guidance.

I also attended the meeting of the -- it is like a short group meeting, the annual meeting being in the spring, of the Association of Professors of Human and Medical Genetics that have come up with some general curricular guidelines for undergraduate medical students. Many of these organizations are focused on a variety of curricula content issues for undergraduates, graduates and many professional organizations working on genetics content in pediatrics, in OB/GYN and the list goes on for all of the specialties. We are trying to at least collect information from those web sites.

The industry and private sector should -- their, if you will, ability to be in many, many places at once should not be underestimated. Many of the companies that are involved in genetic testing, in fact, have been putting a great deal of content on their web site and in the form of at least information, if not elevated to the level of full blown education. There is certainly a great deal of activity out there.

We also are looking at the advocacy groups and organizations, each one that may have specific information, disease-related or disorder-related, others that have a great deal of broader implications.

We had our conference call and, as I say, we have attended several of these meetings to make sure that people know that we are watching.

The work group's approach at this point, undeterred by the enormity of what we might take on, we have decided to forge ahead in a few areas and are looking to the Secretary's Committee as a whole to help guide us. In our discussion on the conference call, we, in fact, determined that one of the best approaches that we might take is to, rather than saying so much of what is the global issue of who needs what exactly, maybe we should look at this the other way around, more from a deficiency model, if you will.

Where are the major gaps that we are seeing right now, either in work force issues, in curricular issues, curricular support and/or training. Are there groups that are not paying attention that should be. If we work at identifying some of those deficiencies with some clarity, we might be helpful to the Secretary in making recommendations about support for additional genetics professionals work force analyses or in the genetics and primary care initiatives that are being funded, are there ways that we could address improving or making the gaps smaller because it has been recognized as a need out there.

This, I think, helped us a little bit in focusing our efforts. Nonetheless, if we keep our audiences broad, the deficiencies can be somewhat overwhelming when you start looking at some of these things.

We decided that what we might do is somewhat of a two-pronged approach with the deficiency model approach being our focus for potential recommendations, but, in fact, the collection of some information and some evaluation on best practices. Which groups out there do we believe are doing a good job of addressing some of the questions and issues most effectively? Where are those major deficiencies and what are the most pressing needs at this point in time and how might we, in fact, assist the Secretary or the federal agencies in helping to address these issues.

I have listed here what I refer to as other activities. It may actually fall into the approach that we have determined I think it was in your folder today is a pretty sparse outline, if you will, of what we think we could begin together in the form of a status report or a snapshot

view that would include a kind of compendium of current efforts and breaking those down into medical schools, other professional organizations, NCHPEG, possibly, in fact, a variety of health professions in those areas, talking about accreditation and residency training for a variety of physicians and then talking about genetics professionals and the needs there and, in fact, looking more directly at the HRSA work force analysis approach and where they are on those that Michele, hopefully, will give us a brief update on what the focus there is.

Some trends and some data about where we have come in the last few years in the training of board-certified health professionals, including the Genetic Counseling Board, as well as other boards and then do some synthesis about the best practices and the gaps.

In thinking about this, though, we aren't always going to have a Susanne Haga and a Secretary's Committee that has a work group that has even the resources of a staff that is as highly competent as they have been and tireless in their efforts. It raises the question again about what format a clearing house or a gathering place, how that fits into the agencies and/or the Human Genome Project or service agencies and where that balance might be and how we as the Secretary's Committee can promote that kind of interaction a little bit better.

Then, actually determining who might be charged with doing some ongoing monitoring and continuing updates of the best practices that are out there given that the work group is at least my understanding is an ad hoc group. We have not been duly appointed for life and that it seems that one of the things that this group could do is have some useful discussion and provide ideas about where these kinds of information might be collected, kept, and how they might be passed on.

Then I think we might be able to develop some recommendation suggesting some mechanisms or programs or additional resources that could be brought to bear by the Secretary in a variety of the organizations here to, in fact, not only promote but enhance this partnership between the consumers and the providers in this time of, as we all well know, very rapid change.

That is really where we are now. The good news is that undeterred, we have done some things, the research and the rapidity with which that research is transferred into the sector, I think, is also good news. I guess the bad news is that curricula and training programs tend to move at the speed of academia, which doesn't quite keep up with the research end of things and I think we need to figure out how we can bring those two things more in alignment.

Michele, maybe do you want to --

DR. PURYEAR: Let me give a quick update and if anybody has some specific questions, the person who is actually writing the proposal happens to be here, but the proposal is going to be a little delayed, probably not until January maybe, but most likely February. There are some difficulties with looking at work force because if you are doing it scientifically you need data and I think that is probably some of the problem with the proposal.

There is a very broad advisory group that is advising about the work force analysis and you are looking at two issues, both supply, which is probably the easier part of the analysis, but also trying to look at the work force in terms of demand, which is the harder part. There are several different scenarios they are setting up or proposing to actually look at demand.

I am trying to remember some of the -- do you want more specifics than that?

DR. BOUGHMAN: I am not sure that we need specifics than that right now, unless there are focused questions. The demand of faculty at a university is really quite simple. It is I want it. I want it now. I want it here and I want it free.

DR. PURYEAR: But they want demand in terms of services, too.

DR. BOUGHMAN: In trying to frame that in a scientific way, testable or data collectible way is extremely difficult and I recognize that we need to, in fact, have the analyses in such a way that we know what it is we are actually analyzing and what the results might actually mean.

DR. PURYEAR: It is a very broad-based analysis of supply, though, from physicians to public health, lab, to allied health professions. I know that is not the right word to say for allied health professionals, but --

DR. BOUGHMAN: Wylie, do you want to make a comment on the primary care initiative? There are others in the room, obviously, that are very involved in that, too.

DR. PURYEAR: That just got launched in September and Wylie can talk about it more specifically, but two things that you point to that I will point out, there is an ongoing evaluation of that project from evaluating both the process and the outcomes and there is also a curriculum that will come out of that that will by the time the project is finished, will have been field tested in 20 medical schools. But that is focused just on physicians.

DR. BURKE: Actually, I will make one more comment about that and then tie it back to some more central stuff that we have been working with on the Committee. The Genetics and Primary Care Project is a faculty development project. So, we pulled together 20 teams who met in Chicago to launch the project and launch the model curriculum.

I would say the word that came out of that that I think is most important is relevance. That is, what really needs to happen in genetics education, whatever target audience you are after is the relevance of new genetic information to that target audience. So, that is a lot of how we built the bridge materials and I think the feedback suggested that that was the right way to go. A lot of other people in this room were there and can comment, too.

If I take that back to stuff that we have been talking about most of the day, a central concern for SACGT is what kind of information should be available about a test, pre-market and post-market. So, that has implications for what kind of pre-market test review you do, but also what kind of data collection and what kind of organization and diffusion you make sure happens.

I would suggest that as we do that, we are creating the raw materials that illustrate relevance and that, as we get a professional language version and a lay version of those,

those become very important elements that we then ought to encourage. One of the outcomes of that process that we should encourage is that those materials made first for safe use of genetic tests really translate into educational materials, pieces of the curriculum that should be made available and actually consciously developed with that in mind.

DR. BOUGHMAN: I would urge you to at least look through the materials that are in your green folder and in your notebooks because, in fact, both on the federally-funded projects that come from a variety of agencies and just the partial listing of web sites available, I can tell you can -- and some of the amazing content on those sites. It is actually very impressive. I think it is well worth every Committee member's time to at least have a good sampling of the kinds of things that are out there.

DR. BURKE: If I could just comment a little more, one of the things the Genetics and Primary Care Project will be doing is -- we are encouraging the teams to do is actually look at web sites and figure which ones are useful. I agree, there are some incredibly wonderful web sites that produce invaluable materials and I think part of the whole educational process, it seems to me, is just cataloguing what is out there, sort of figuring out what is out there. Some of it is bad though. I mean, there is good stuff and there is bad stuff.

So, I think, again, our role in sort of encouraging a template might be helpful. There probably is also a screening role that somebody needs to take on.

DR. COLLINS: In that regard, there is this organization called GROW, Genetic Resources on the Web, which is having its third meeting at the end of this month, which is a loosely knit organization of groups that are interested in seeing quality information about genetics up on the web in various places and learning from each other about where the gaps are, which is a serious question.

There is some very good stuff, but there are also some large holes. Also, part of this effort is to try to focus on quality of the material, as well as making sure that what is up there is objective and not unduly influenced by advertising needs and, therefore, sticking with one of

these codes, like the HON code, which is what GROW seems to be presently primarily enamored of as a way of assuring that this is objective information.

That meeting, which is going to happen November 30th, December 1st, has a bunch of additional paths in front of this group to try to figure out how to put together a search engine that allows you from the sites that are felt to meet these criteria to be searched from one place, which currently is not so easy to do. Certainly, the usual search engines don't necessarily get you what you are looking for, as well as a host of other issues.

So, this group while it lacks any formal structure, other than sort of good will and Alan Guttmacher as the leader sort of keeping it rolling along, is trying to look at this issue of how to see what is out there and make the best of it.

DR. BOUGHMAN: Well, and that is one of the organizations that we need to be very much aware of. Given that there are even gaps in the knowledge, I am going to ask Judy if she might make a comment or two that there are still some challenges we have even if good information is out there and translating this into some of the non-genetics, at least board-certified kinds of personnel and the way that your experience at the recent meeting in Baltimore might shed some light on the challenge.

DR. LEWIS: The meeting I was at in Baltimore was looking at nurses and nurse educators. There were clinicians. There were deans of the top schools of nursing. There were faculty members. There were researchers in the area of genetics and our goal was just to get together and get a sense of what is there, what are the gaps, and what are the issues.

There were several issues that came out and I agree with you completely on the issue of curriculum. Part of what happens is every time you put something in, you have to let something go and nobody is willing to let anything go. The curricular issue was actually the easier issue because it is somewhat controllable and there are accreditations and there are standards.

The more difficult issue is the issue of clinicians in practice and the diversity of clinicians in practice, ranging in my discipline from folks who appeared at the associate degree to folks who have doctoral degrees and looking at some of the models that are out there in some of the schools, looking at credentialing certification and not necessarily wanting to create a whole lot more hoops, but just having a sense of the fact that it is a very, very diverse group and that is just within one profession. When you add to that, the other professions -- you were at the meeting, Michele, did you have any different perspectives?

DR. PURYEAR: No, but the meeting was in Bethesda.

DR. LEWIS: What did I say?

DR. PURYEAR: You both said Baltimore.

That was the meeting that was sponsored by NIH and HRSA. Actually, the proceedings of that will be published shortly and they will be making recommendations about next steps for nursing.

DR. BOUGHMAN: Which brings me back to my request from the chairman here to help the committee members figure out where we go from here. I think we still have some discussions to have about putting in some sort of readable format some of the information that we have learned. But given the breadth and depth of this issue and that it will never be brought to closure actually, I am going to stand here and admit that it is still clear as mud to me really what the Committee would like for the work group to bring back to this group, recognizing that genetics education will continue to be an extremely important issue.

But I think, Ed, that this goes back a little bit to the comments that you made first thing this morning, that our agenda doesn't seem to get that much smaller. It seems to continue to be larger. I have seen a lot of the same names up on a lot of work group overheads today and I would like some guidance so that when we get together again by conference call or whatever we can gain some focus and provide the output that this group wishes us to provide.

DR. MC CABE: I would think one of the things -- I will throw something out and we can discuss it, but it seems like you have put together a compendium, recognizing that it would be impossible to do a complete compendium, but you have done a compendium of what is available, various media, what are some ongoing activities dealing with issues around education. It would seem that it would be good to summarize that in a white paper that would say -- because you have also identified gaps and where there are needs -- and to bring that back for us to review at the next meeting and then distribute to some of the groups, some of the groups funded by NHGRI and other groups, to get input and feedback before finalization, again, recognizing that the importance is not putting all down what is available, but I think as you have identified where the gaps are and looking at are there recommendations then that we can make to the Secretary about ways that HHS could help to fill those gaps.

Perhaps some who are more involved in this than I am could comment on it. Francis, certainly with the ELSI efforts, you have been doing a lot of this and a good bit of the material has been grant funded by the various agencies to deal with education. I found it quite interesting reading through that information.

Would this be at all helpful, do you think, Francis?

DR. COLLINS: I think a lot of work was done to put together this assembled information and it would be nice to include with that some sort of a white paper summary, particularly focusing on areas where in your survey you found there were things that were not happening that should be. There may be additional things not uncovered in your search that could also be added into this to make it more complete. So, it would be good to circulate it around a bit amongst some other eyes before finalizing it.

Then I would think in terms of making a recommendation to the Secretary about interventions that might be helpful, that would be something that this plenary group ought to think about. What could at the level of the Secretary of HHS be done to encourage this process forward. Most of what is going on right now is not actually governmentally organized except in

the sense of various research grants. But the organizations that hare taking this on, things like NCHPEG are not themselves government organizations.

The funding for NCHPEG is coming from a cobbling together of various sources. HRSA has obviously invested a lot of their resources in getting education up and going, but is there a missing piece here that we can perhaps ask the Secretary to take charge of? I am not sure I clearly see that right now, but having such a white paper would be helpful.

DR. KHOURY: First, I would like to commend Joann and the group for delving into what might look like a bottomless pit here in terms of not being able to climb out of it, but I would like to offer a suggestion or two, following up on the theme of Wylie in terms of relevance.

One of the things that this group can focus on at least in the next few months and come up with a product that can synergistically interact with some of your other recommendations around genetic testing, other than just genetics education in general.

So, you have identified a framework by which we can begin to see the transition from a gene discovery to applicability in both medical and public health settings. So, if you can focus in your efforts on the educational pieces and the gaps that are needed to make that transition effective, relevant to the various audiences from allied health professionals, including the public health community, which we and the CDC have been focusing on to a large extent.

I think there is a lot of recommendations you can make to the Secretary that would be cross cutting in nature, that will affect all of the agencies and will lead to some forward movement that will be very synergistic to the other recommendations you made.

So, I am not saying all these other areas are not important, but there is so much you can take on and I would recommend that that white paper would be a little bit more focused and everything.

DR. MC CABE: One of the recommendations that I have thought of and I think Sarah and I talked about this as we were going around, we have talked a lot about education and

we have talked about educating every human on the planet at various times. One of the things that I think an area that we could focus on is educating the appropriate individuals in the agencies because there are parts of these agencies that really are going to be taking on responsibility for genetics, that they have not -- they were trained when many of us were trained, before genetics. So that one area that we could focus on is really identifying individuals within the federal agencies to educate rather than trying to cast the net quite as broadly as we have at some time in the past.

MS. DAVIDSON: At the risk of broadening the topic instead of just trying to narrow it, I have been sitting here just thinking about public education and, just myself as the consumer or Elliott as a consumer, any of us or our neighbors or my children being faced with a test and what the experience is for them.

I am not sure whether this list really gets to it. I am on the committee but I would like to have us if not now then at some point really get to the point of being able to look at what is available not only on the Internet because people get information through all kinds of mediums and some of them will be from professionals, but I don't think that we have any grasp and I say this today from the Genetic Alliance's perspective because certainly public education is something that we are very involved in.

But I don't know of anyone who really has a full grasp of what the experience is like for different people coming from communities, different language backgrounds, different ethnocultural backgrounds, what that experience is like. My sense is that there are huge gaps there. I think that is an important topic for this committee to take on.

DR. KOENIG: I am going to try and do two things, follow up from what Ed just said about making this list more specific, but also trying to look forward a little bit to tomorrow when we try and set some priorities and talk about areas of overlap between the different teams and work groups.

One of the things that the informed consent team has talked about is the need for IRB education. That is a group that seems to be missing so far, unless I didn't really connect with something in your plan, and that is, again, like agency officials, it is a very targeted group that I think is extremely important because the way -- when I present tomorrow, I am going to talk about the issue that the IRB is really the first stage of the oversight process of genetic tests in general. So, I think that is a particularly important group to educate and from what we have heard, there are a lot of gaps.

So, I think that is going to be an area that needs coordination.

DR. BOUGHMAN: I think you are right. IRB did come up in our discussions but in fact we had plenty of other things to spend a little more time on. However, going back to Muin's comments about from gene discovery through the translation into services, the IRBs would be an identifiable step in that process and, therefore, a targeted piece. I will be taking notes tomorrow to see how we can, in fact, interact on that.

DR. PURYEAR: From the HRSA perspective, we would find a set of recommendations to be very useful, especially if they were very targeted.

Earl Fox has identified for HRSA for the next year's budget -- genetics is one of three emerging priorities that he is targeting and has included legislative proposal for that for both the agency as a whole, but also specifically for the Bureau of Health Professions. We certainly will use the work force analysis to inform that process, but more specific recommendations would also help target where that money should go.

But even narrowing it to genetic testing, I feel, though, that is still -- I mean, the process of genetic testing involves a very broad cadre of health care professionals and public health professionals in general. So, I don't think we have narrowed when you talk about a genetic test or testing. I mean, it is still just as broad. But I do agree that whatever we are doing, we should be informing the process.

For instance, I think what we find out with the genetics in primary care process or project, that actually we should probably at some point along the line when we have something include FDA because I think that might help the labeling process actually and what should be a part of that.

DR. CHARACHE: Barbara has covered what I was going to say. I am concerned about the IRBs, not only from the point of view of their ability to provide appropriate oversight, but because I think we have to be targeted towards providing guidance for the researcher early in the course of their study design so they don't get caught short when they want to go further later on.

DR. BURKE: I think the work of the Education Group so far fits perhaps with previous conversation in saying that the idea that genetics education is important seems to be out there. So, this sort of why do it, I think, is a question that we don't need to address. It is already being addressed, but I think there is -- my sense from personal experiences and I think it fits with a lot of the projects we are referring to is that there is still some work around what, what should be the content of education and how should it be done. Again, sort of in terms of focus for our Committee, it seems to me we are working hard to define the what or at least to create an organizing template that defines the what.

So, it might well be that, No. 1, we offer that fruit of our work as a guide to this is what we think is relevant for test users and then propose that there should be an interactive conversation, which says, okay, if this is what is to be taught, how is it to be taught. That is probably a creative conversation between us offering some ideas about content and educational specialists some concepts about how to get that stuff across. But I think the content concept is an important one.

DR. LANIER: Joan,, you mentioned in your outline and we discussed in the work group the issue of outcomes assessment. I think we should talk more about that. It seems to me that one of the things we could offer -- just to say that there are a lot of education programs

available, a lot of information available, but we in some ways can have a method of assessing whether it really changes practices of the clinicians or of consumers and have that as a feedback to make some distinctions among all the programs that are available, curricula and the education side.

DR. MC CABE: Why don't we hear Judy and then we can talk about that a little bit more.

DR. LEWIS: I wish I had confidence that education changed practice. I am not sure I do have that confidence, speaking as somebody who has spent their life as an educator. And I don't think we want to get into the standard setting, but I think one of the things we might want to be able to start to focus on is recommending that professional agencies work to set standards so that the public has some sense of what the difference in competencies are because there are so many different kinds of health care professionals one could go to for genetic information.

If the various specialties had some set of standards as to what should a generalist physician know -- and I am not saying we do this. I am saying that the professions do the standard setting, but then what we talk about is that we recognize the fact that some of us who were trained in the pre-genomic era and that therefore there should be some standard setting and do some encouragement along those lines, that that might be a contribution we could make in a white paper.

DR. BOUGHMAN: Well, let me say as a chief academic officer, I bring a slightly different perspective to the educational forum. There has been a major shift in the last decade, I believe, moving from the course approach to the integrated in the curriculum approach to the competency approach. The competency approach incorporating skills, knowledge, and the actual use and practice, the attitudes, the appreciation that then making a transition into practice, competencies being able to be, if not measured, at least plus/minus assessed, even during lifelong learning processes, not just during one's degree-seeking years.

NCHPEG, the Association of Professors of Human and Medical Genetics, and many of these other organizations are really taking much more the competency approach, I think, which is one of the things that we can capture and one of the things that I have noticed in reading through these things and I think that is an important shift for us because competencies tend to be able to be more applicable across professional lines than how is it going to fit into the first- or second-year curriculum.

That just doesn't translate easily.

DR. TUCKSON: Yes, I think that last answer was very good. I think Judy raises a provocative issue here. I think that I sort of sound like Elliott, which is a good thing, but in the sense that inevitably this stuff is going to be so integral to the practice of the professions, particularly for physicians -- I think it would be very tough to be able to be able to tease out exactly how this is different from the practice of the profession in medicine in general. It is so intertwined with each passing day.

I think what I like from the answer is that, not only is it the group that you mentioned, but everyone of the boards, everyone of the specialty societies, everybody is focusing now on the determination of competence in a new way that is well beyond what used to be for the traditional board certification.

So, I think that that is where the answer really is here. Given the inevitability that genetics is going to be -- I think Francis's quote, which is -- there ain't no medicine unless it is genetics. So, bottom line is I think that is the way it gets done.

DR. BOUGHMAN: Reed, I would say -- I am on that ABMS Task Force on basic physician competence. So, I have been working on those six basic competencies now for about three and a half years. I tried to get genetics right in there along with a variety of things like the ability to hold patient information confidential. They didn't go for genetics being quite that basic to all medical practice, but it has been tossed out there. In fact, I know that the 20 plus

members of the American Board of Medical Specialties are -- that is one of the things that we are trying to capture from each one of those boards.

DR. KHOURY: I guess I keep coming back to the point mentioned earlier. Although, Michele, I agree with you that by focusing on genetic testing, we still haven't narrowed down a very narrow angle, but I think we can considerably focus on the task at hand and I would, again, urge the committee to make your work easier for the next few months by focusing on the framework of from gene discovery to medical and public health practice and focus on the relevance of what exists out there in terms of who needs to be educated and what for in terms to make that transition a reality. In other words, there are many examples where people don't need to know how to find a gene. They don't need to know gene mapping. They don't need to know a lot about linkage analysis and LOD scores.

We are finding that out when we talk to the public health professionals, who are out in the field trying to look at programs and policy and reimbursements and things like that. But I have heard many examples from just this discussion around the IRBs, the federal agencies. I would add state public health agencies to this mix, the primary care physicians. How do we collect data? What does it mean to teach people about analytic and clinical validity?

I think we can come up with a document that is highly synergistic with what you guys have been working on for the last year. Not to minimize everything else that is going on because that is very important, too, but to make a set of recommendations that would help the implementation of this new paradigm of oversight that you guys have laid out on us as federal agencies.

MR. HILLBACK: I would like to sound like Reed for a minute. No, I think just sitting back and listening to this for awhile. I liked where Muin was going, actually. I think this almost feels like we ought to be defining this like an onion with a lot of layers and then try to think about each one separately.

I have been making a lot of noise over many years about this education, but I think when you use the big word education, it is so mind boggling that you can't get your arms around it and you can't even think about it. So, I like where Muin was going, that maybe one of the things we should do is break this apart into a number of different layers, starting at the core with those people who are really instrumental in what is going to happen in the next five years in where we are. That includes agency people, that includes state people, that includes IRBs. Those are key places we have to start. It includes some look at the primary care physicians, but in a different way.

But take each of those groups separately and try to see where we can do something and when we get to the general population, that is the outer layer of the onion. I am not sure that we have the resources or the focus to try and deal with that, as much as I would love to try.

So, maybe that is one way we can get a handle on it is to break it into these pieces and try to look at each one separately, totally separately.

DR. MC CABE: I think also your statements that you were making, Joann, about the competencies, as you formulate this into a white paper, it is going to be important to talk about competencies and not just the broader -- where education is going, at least professional education, because it also defines process to some extent, as well, which people are beginning to do, which tends to be more case-based, more specific and give some examples that one can get hold of better.

DR. PURYEAR: Muin, I don't disagree with you. I just wanted to make sure that you understood that I thought that was a very broad task.

I think we also need to distinguish between whether or not we are talking about education or if we are talking about training programs because that is, I think, a big difference in the task that you are undertaking. I think we actually need to engage in training programs and not just broad-based education. I mean, we need to be very specific and very targeted.

DR. MC CABE: Anything else?

DR. CHARACHE: I am also thinking over here of the need to tie this into practice, to have the capacity to have a case orientation for information. I mean, how do we get the information to the practitioner who has ordered a test and has gotten back some information that he is going to have to share or a patient wants to look up a specific disease and it may well be through an Internet dedicated or whatever, but I think that this is a very major need when we talk about the use of genetic tests in a practical sense. It really is almost case-associated ability to gain information you need it for very busy people.

DR. BOUGHMAN: Joann, you have been taking notes, do you want to summarize perhaps what you have gotten from this because we have been throwing ideas at you. I don't know that we have made your task any easier.

DR. BOUGHMAN: Well, actually some of the notes I have written down is -- I have two master's projects outlined for students already here. Don't you think it would be a great master's project for a genetic counselor to scan in all of the competency-based formats that are now out there and cross-reference on key words after they are put into a database to see what commonalities come out and build from there? I think that would be a great way to look at some of the things that are, in fact, in common and come back to each one of the professions and how they feed into this process.

I think that what I have heard is, in fact, a vote to keep going on putting together at least snapshot, if not compendium, certainly not complete, but to try and put together in a white paper a kind of format with identification of some of the needs and gaps that focuses on the steps of the process, at least of genetic testing to start with. If we say an "oh, by the way," in general that might be all right as well, but try and identify some of the points in that process for the providers or the other partners in this process, the consumers, where we think there has not been activity going on. Then if we can provide a focus for the Committee as a whole to come up with some recommendations on how we might suggest to the Secretary that agencies or other

groups might address some of these issues, that that would be a good place for us to come back at our next meeting.

So, we will try and get something together and start circulating it and see where we go from there. All ideas are welcomed. You know, what I see as gaps out there are just what I don't know, not what everybody in the room doesn't know. So, we all need to be providing information here to find out where, in fact, the real gaps are, not just the ones that I had there.

DR. COLLINS: That information should go to you, the things that you are asking for?

DR. BOUGHMAN: Either me or Susanne. We communicate on a very regular basis.

MR. HILLBACK: Yes. I guess going back to something Pat said and what Muin was saying before, maybe one of the ways to think of this in a totally different way is to go back and think of it from a micro point of view. In other words, put ourselves in the position of an IRB member, put ourselves in the position of a primary care physician and say in the next five to ten years, what do they need to know now, what are they going to need to know and then try to compare that against these various programs and plans that people have to see are they likely to get people there and where the gaps might be.

But by taking a micro look, I think we can all kind of get into that body maybe easier than we can as in a macro look. Maybe that is another way of trying to work back at it and put a unique point of view on it from the Committee's point.

DR. MC CABE: So, one of the things you might think about doing, again, as part of this, just as we were talking about testing out some specific cases with some of the other models that we were dealing with earlier, you might identify some of the cases, as it were, individuals who need educating, who we have thrown out at you and look at them very specifically.

DR. LEWIS: I was just thinking of a cross section between the access issues and the education issues and wondering if we had done anything. And I can't remember. I am sort of getting brain dead at this point in the day -- looking at materials and languages other than English or materials that are appropriate for specific other groups and that that might be something that, as we put our compendium together, that might help us identify some gaps so that we may have a lot of material, but we may not have material that is accessible or acceptable for some groups.

DR. BOUGHMAN: In fact, there have been identified on some of the web sites and -- I don't know that they would be full primers, but some of that I know is available, at least in Spanish. I don't know about some of the other languages and some of the disease-specific kinds of things might begin to -- but we did not look at that issue specifically but obviously it is an important one.

DR. MC CABE: Good.

We are going to move on now. Thank you very much, Joann and committee.

Open Discussion

We are going to move on now to an open discussion for about 35 minutes or so.

We have two items that we had talked about this morning of needing to come back to. One is the model for scrutiny and the other is the patent letter. I am going to make a decision that we focus on the model for scrutiny for the next 30 minutes and that we put the patent letter off until tomorrow. But we still are going to work on both of those.

MR. HILLBACK: I agree because I think we can get some written things to Sarah this afternoon because we have been working on them and have a better chance at the patent letter tomorrow that way.

DR. MC CABE: Right. And if we have some loss of individuals as the afternoon goes tomorrow, we can still continue on the patent letter. But I really want the input of the entire group.

So, let's go to those models for scrutiny. Do we want to start -- what is the Committee's pleasure?

DR. BURKE: I am just going to propose that we -- if we can on the overheads -- put up Muin's revised and our original one and it seems to me we have got three points of discussion. One, I think, we can resolve fairly quickly, but that has to do with using number of tests done as a threshold versus disease prevalence. Then there is the issue of what is a diagnostic, what is a predictive or is there a better way to define that and then there is the issue of do we need to keep in those descriptors to define bad predictive tests or more worrisome predictive tests.

DR. MC CABE: Okay. So, that will begin to focus -- if we could get those overheads up there.

DR. PURYEAR: This is a little PSA. Sarah Carr's husband, George Carr, is going to be on TV tonight at 10 o'clock on Channel 26. He is a world famous sculptor. Everybody should see it.

DR. MC CABE: So, this is then Muin's, right? Do we have the other one? Why don't we leave Muin's up there and everybody find your hard copy to look at. Tab 2, page 4.

DR. LEWIS: Can I just start off by saying I don't think number of tests per se should be included in the model? I would like to suggest that we move that because I really think that, as I said earlier, that that doesn't necessarily tell me that scrutiny isn't necessary. I think reliability and validity testing is just as important, small volume versus large volume. I know it is a matter of the greatest good for the greatest number, but if you are one of those people who needs a smaller test, I would just like to see us remove that.

DR. BURKE: I would second that on those grounds and also on the grounds that three different working groups couldn't come up with a good way to do it. So, we just don't have a handle on that.

DR. CHARACHE: I would like to third that for a different reason, which is because of the tremendous shifts in numbers. Now, where they are doing ethnic-based testing, all of the sudden a rare disease is screened for large numbers. So, it is not a stable concept.

DR. MC CABE: So, then we would go -- how about using intended use as the first cutoff? This deals with saying that population-based versus diagnostic versus prenatal, that one can tailor then the subsequent algorithm based on the population base. It does create a problem though because it says that the same test may undergo different algorithms depending on its use.

DR. BURKE: The issue really -- I mean, if you start with population-based as the first cut, it makes a lot of sense. I mean, I think we could all agree that if the test is being proposed for population screening, it needs a higher level of scrutiny for all those reasons of implications for number of people tested and methodologies and so on.

The problem is going to be -- and I would propose, therefore, that we keep that. I don't think it is going to kick in very much except new newborn screening tests because, certainly when you are talking about adult health issues, health issues after newborn, most tests are already going to be approved and in commercial use before they develop a consensus to universal screening; hemochromatosis being an example.

Nevertheless, I still think it is appropriate to have that step there for that relatively small number of tests that will be introduced initially as a population screen. I think those should receive a different level of scrutiny.

DR. MC CABE: The question I am getting at is that you wouldn't only kick in if it was population-based, that there would be a different algorithm that one would have to deal with. Does that sound right?

DR. BURKE: I think I would propose that we can agree that population-based should be an automatic shunt to a particular screen. Whether other uses, such as prenatal testing should be as well, seems to me something that we heard we need to talk about.

DR. MC CABE: Okay.

DR. LEWIS: I just wanted to talk about the prenatal issue. Is that okay to do at this point?

DR. MC CABE: Well, if there is some follow-up specific to this and I know Francis, I think, has some specific follow-up to this. Muin, is yours follow-up to this also, this point that Wylie was speaking to?

DR. KHOURY: Yes.

DR. COLLINS: I was just a little confused, Wylie, by what you said in terms of tests not coming down this particular pathway except maybe for newborn screening. I guess I had understood that if a test, such as hemochromatosis, which had been in common use in the circumstance where there is a family history and so you are looking at a high-risk individual, if you were going to move into population screening, it would still travel through this flow chart.

DR. BURKE: I guess we need advice from FDA on that point.

DR. COLLINS: Otherwise, it would be off-label.

DR. BURKE: Yes. Is it possible to bring it back to FDA at that point as one of the barriers that has to be overcome?

DR. GUTMAN: Well, everything at FDA you have to recognize is claims driven. So, the angst that has been felt by the various groups about the possibility that somebody would perhaps attempt to inadvertently or deliberately gain the system by picking the most limited or the most safe or the lowest scrutiny claim is absolutely fair game. In fact, maybe you will be horrified to know this as we are looking at new technology, we actually encourage sponsors to do that, to get a product out in the market, that we are very claims driven.

The issue would be whether you would be so upset about the potential for the broader claims or the off-label use, what options you would have to try and prevent that or to redirect that. From my review of the history, I am frankly quite comfortable with having products labeled for what they do and what they don't do. If I worried about everything that a product didn't do, I would have a nervous breakdown and wouldn't be here.

DR. MC CABE: Francis, did you have a follow-up?

DR. COLLINS: Just as a follow-up, I would think, based on the discussions we have had about this issue in the past, this group would feel uncomfortable if a test is going to move from a high-risk situation to population screening, if it didn't come back for this process.

DR. GUTMAN: Well, it would have to come back to make the claim. What I am suggesting is that if there was some way that it could slip into practice without being -- I don't know if I have ever encountered anything like this. If you had a biochemical test, for example, that was suddenly used for screening without the claim, I don't frankly know what our legal authority would be in terms of stepping in and saying to the State of Minnesota, you can't do that as a matter of practice.

DR. BURKE: I think we can just give an example and that is HFE mutation testing. HFE mutation testing became available, I think, for reasons people would find very acceptable for identifying within families. Now there is a public debate going on about whether universal screening should occur. Clearly there is no decision on that but if five, ten years from now there is an agreement that we should screen for hemochromatosis and HFE mutation testing is the right way to do it, it won't come as a laboratory claim. It will come as practice guidelines from professional organizations. It won't be a claim from a lab.

DR. KHOURY: I think we are hitting the essence of this discussion whereby the pre- and post-market phase type distinction breaks down because of this off-label use. There are very few tests, like maybe newborn screening, that are initially introduced, like by Myneugen and some other groups to screen all newborns for these conditions. Most tests would come in

slowly. They would sneak in, starting with families, then healthy relatives and then, et cetera, et cetera. And there would be that off-label use. They may or may not come back to the FDA for another pre-market because they are already in the market. That is why we need that public health driven post-market analysis of the kind we have been talking about.

So, there is no problem in my mind to make that a public health priority, to watch out for those tests that are going to begun to be used on large segments of the population. When we did this analysis, if you see the other chart, there are a few of them that way, not only hemochromatosis but karyotesting for CF is another one when there was some consensus development building that came to it. The so-called Ashkenazi Jewish panel, for example, and those things are not dropped into the market with the initial intent or very rarely with the initial intent of population screening. So, this Committee has to see what the FDA can do and what the post-market analysis can do and somehow meld them together.

But if the initial intent -- and this is all driven by intended use and to paraphrase what the FDA says, claims to be used for what population or for what use. Then the pre-market approval process kicks in, but there is a lot of off-label use will go on after that and I am not sure how much control the FDA can have.

DR. GUTMAN: But what Wylie says is absolutely right. If a test crosses over as a practice of medicine, if it is able to do that, to be marketed without a change in the label, that is likely to happen. Where they will tend to come back in for FDA to change the label is if they think it provides some marketing advantage or some advantage in terms of legal standing. That will happen, particularly in competitive areas or, for example, a wonderful example of that is PSA. PSA was originally approved for monitoring. The use of PSA for screening started to occur in the mid to late eighties. Nobody came in. Actually the first company came in with approval in 1992 and we couldn't figure out why in the world they came in since it was being universally or widely used all over the place and they came in because they wanted to be able to say there were the first FDA approved device specifically for that purpose.

MR. HILLBACK: The list that Muin gave us earlier with a number of tests on it, when you sit and look at things like Gaucher's disease or Canavan's or Tay-Sachs and say, well, wait a minute, I mean, the reason we launched this test originally was diagnostic and not population-based and not prenatal. Now it is all of the sudden over here in a Level 2 list on this other version of this that he gave us and CF is there and sickle cell and a bunch of other things. They didn't start off as let's do this for the entire population. They started off as we know a little bit about this disease or this genotype-phenotype relationship and we are going to start using it to diagnose and, oh, gosh, now that we know more, let's start using it more broadly.

I don't think we are going to find it easy to do that. It is somewhat easier to go between diagnostic and predictive, although I am not sure it is totally simple to do that either. If the first use is predictive, which for a lot of things it will be, then it is pretty clear where you start, but for things that start off as clearly a diagnostic test -- this has been very interesting to me to see this list that Muin put together because it kind of hit me with a 2 by 4.

DR. MC CABE: Judy and then Pat. You had comments unrelated to this discussion.

DR. LEWIS: I think the issue of prenatal diagnostic testing, which is what it is called, so, therefore, it is diagnostic, I mean, I think, we tend to think of that as a special situation, but it is a situation where there is a diagnosis and an intervention. The intervention is a pretty profound intervention and I think given the social construction of society right now, it becomes a hot button. But I think that if we focus on the hot button rather than on the science, I think there are two separate issues. One is giving people information. The second is what people do with that information. But if we have information that is diagnostic and some prenatal tests are screening, like if you look at how the Down stuff started, it started out as -- the first level is a screening test and depending on what happens in the screening test, then you go for more diagnostic tests. But I think we need to have good information and we are making profound

decisions and some would argue that the decisions that we make on all health care situations are equally profound.

So, I think that the prenatal piece, to treat it as a special category is dealing with an issue that is separate that is separate from the medical sciences, dealing with an issue that is a social issue right now. As somebody who deals with pregnant women all the time, I just think that if we make it into a special category that we need to be real careful because it is diagnostic information that you are giving to people who are making health care-related decisions that are pretty serious.

But I would argue that some of the other health care decisions we make based on genetic information are also pretty serious.

DR. CHARACHE: I actually am on the same subject but I am just having a great deal of difficulty because of the continuum. We are trying to make three pockets, where it really is totally continuous. It is diagnostic in me but it is predictive in my family, who are asymptomatic. I think it is a very difficult cut to make and I think in a real sense because of the way tests become screening tests, whether it is for an ethnic group or whether it is for whole populations. I have a great deal of difficulty seeing where to cut.

Now, I think the reason for doing this in the first place had two goals that I am remembering. One goal is not to overly burden a small unit unnecessarily if it is not really necessary. The second is to decrease the burden on the FDA by not overloading them with so many tests that they can't do a good job. In terms of overloading with so many tests that they can't do a good job, the last thing that Dave and Steve are going to want is for us to say you have to review this every time there is a change in intended use. That is not going to off load them and it may be very difficult.

I am wondering about -- and I just put this out -- a totally different starting cut, which is to separate those tests that are developed by industry from those tests that are developed by laboratories. Let me tell you why. And I didn't say which laboratories, all the home brews.

I think we can predict that all those developed by industry are going to be high volume or they wouldn't bother. So, that may be a very smooth way of --

DR. MC CABE: I would argue that there are examples now where that isn't the case.

DR. CHARACHE: Okay. I was just trying to see how to get off the slippery slope because I am sliding.

DR. MC CABE: I think that what we have is we have a model that was developed out of a working group that included laboratorians, as well as others. It was reviewed by this group. It was then tried by the Lab Forum. It didn't do that well there. One of the key problems with it was the volume, but it looks like we may have a way around that. So, I guess I am arguing that we not start all over again.

DR. CHARACHE: I wasn't going to start all over again. I was just going to take the two pieces --

DR. MC CABE: I don't think that --

DR. CHARACHE: Okay. I give up. I give up very fast.

DR. MC CABE: Would we be willing to then use instead of the volume as the first cut, the intended use of the first cut? Certainly, if we looked at population-based as this algorithm, then worked through this algorithm, this would be a relatively small number of tests as we have discussed because looking at the large volume tests in general are ones that we have experience with and there are relatively few here.

DR. BURKE: But that may grow.

DR. MC CABE: Yes, yes, but that is fine. At least you are not starting with 10,000 tests. You are starting with perhaps five to ten so that people can learn the system and not create a huge problem, at least with this algorithm.

DR. CHARACHE: We are going to have to define "population," whether it is a family group as a population or it is screening of everybody.

DR. MC CABE: Everything comes down to the definition. So, ultimately we have to define those.

Then we have the prevalence as the next cut in the cascade. Are people satisfied with prevalence, the numbers that have been chosen here? I will specifically ask Mary since you deal with issues about rare disease, orphan diseases. Are these numbers that you feel are appropriate; 1 in 10,000?

MS. DAVIDSON: I am going to have to ask Muin to help me translate this. I mean, the rare disease, the definition of rare diseases is the incidence is 200,000 in the United States and your translation of that --

DR. KHOURY: If we have 400 million, that is about 1 in 20,000. We are in the ball park. Most of the rare diseases are really under 1 in 20,000.

DR. COLLINS: Wait, wait, wait. We lost a decimal place there. One in 2,000 -- if you are saying 200,000 cases in the U.S. or less is a rare disease -- I think there are actually about 300 million in the country. So, that is 1 in 1,500.

DR. KHOURY: 1 in 2,000. That might push some of them into the Level 2. I think we should use a consistent definition with what the Office of Rare Diseases uses. I think that would be -- or what the FDA uses, too.

DR. GUTMAN: I can't tell you how -- if you put in 10,000, again, we are pushing the edge of the box. You have to realize that our reg is written at 1 in 4,000. It is tests or testing episodes per year, not cases of disease, but tests. So, if you had a rare disease and you are doing a million tests, it doesn't count. You have to have 4,000 or less. The 4,000 is very safe for us. We have an existing reg --

DR. MC CABE: That is for the HDE. This is different than the HDE. We are talking about a different number. So, I think that certainly the HDE issue is one that we have learned about and that will be helpful for some of the orphan diseases. Now we are talking about this algorithm.

DR. PURYEAR: Why would a test for a rare disease need any less scrutiny and doesn't it look like we don't value those tests -- I mean, you have to phrase this in a different way because it just doesn't look right. I sort of understand what the intent is but it is not coming across with this.

DR. MC CABE: Tell us what the intent is?

DR. PURYEAR: I assume you want to make sure that these tests are not hindered and are brought into practice within that small community as quickly as possible but you are also looking like you are saying that they don't deserve the kind of scrutiny that tests for other people get, too.

DR. COLLINS: I think we are mixing up incidents and prevalence in a way that may get us in a little trouble here. So, can we come back to this definition.

The Rare Disease Office defines a disorder as rare if there are 200,000 or less people with the disease at a moment in time. So, that is a prevalence kind of thing.

DR. MC CABE: Yes, it is a prevalence.

DR. COLLINS: So, you can imagine for a condition that is very early lethal that you might have a fairly common in incidence terms, but nowhere near that number of affected individuals. So, we need to think about our definition as we are trying to make this distinction between rare and common. Is it an incidence or a prevalence? I think actually when you are talking about genetic tests -- well, I am not sure which is more logical. It is going to be hard to back into this.

DR. MC CABE: Well, but I think that one of the things that we have talked about is consistency and there is already a federal definition of a rare disorder. Is that the terminology that is used? It is then approximately 1 in 1,500 to 1 in 2,000. That is a prevalence and we have to recognize -- the definition is one of prevalence rather than incidence.

DR. KHOURY: Prevalence is incidence times duration. So, if you have lethal conditions, the prevalence would be low even though the incidence might be high. I think from

the point of view of genetic testing, I would contend that incidence is the more proper way of thinking about this because as new cases come in, you are testing them for diagnostic or predictive entities. I mean, you don't wait for them to be 15 years old or 45.

So, I think we might need to think about this a little bit more carefully than the usual definition.

DR. COLLINS: That is exactly where I was going and it puts us in collision with the current definition, which is a prevalence definition. So, we may not be able to do both.

DR. MC CABE: Does anybody have any experience -- I would ask Muin and possibly Mary about whether there is any experience with diseases fitting the rare disease definition in terms of what their incidences are. In other words, we do have a federally defined rare disease. Do we know how that translates from the prevalence to the incidence? Do we know which diseases fall into that category?

DR. KHOURY: I can do some research.

DR. BOUGHMAN: We come back to your definition of "population" and the denominator there, Ed. Unfortunately, you can't separate the two because, in fact, in the U.S. population, we might have several that would meet that definition, but in a more well-defined population, the incidence would change dramatically.

The other point that I would make is that if we -- and we will quickly run into the diagnostic versus predictive, the carrier situation and at risk in genetic testing and all of that would be related to incidence not prevalence.

DR. MC CABE: Well, I mean, the other way to look at this is to say do away with this common/rare cut. I mean, if you are -- so that you just eliminate that and now it goes to intended use. It goes "no," then intended use and then the split is there.

DR. LEWIS: I think the other thing is right now we are talking about diseases rather than mutations. I think that that is an important point to build on what Michele was saying and especially some of the comments we have gotten from the people who have been working

with us who are members of diverse ethnic populations and when you look at a disease like cystic fibrosis, you have got a relatively common disease in some groups, a relatively rare disease in other groups, and the mutations are very different. So, we have gotten pleas from groups that have different genetic makeups to be sure that we address this. So, we can't just talk about diseases. We have to start talking about mutations for some diseases and then we really could get into the rare mutation category very quickly.

So, I think that maybe this isn't a good cut because it may be different in different populations, but it may be one mutation in some populations and several in others.

DR. BURKE: It seems to me it would be useful in making that decision whether or not we should keep this as a cut, what it is that we are trying to accomplish or what it is that we do differently independent from the other properties of the test. It seems to me the primary thing that we would do differently is that we would have different expectations for how much data needed to be there before we felt we had acceptable clinical validity just because if it is rare, there is a limit to what is possible. We wouldn't want to hold a test up.

So, I think what we may unfortunately be talking about is that under both Level 2 and Level 1, there is a rare disease set of criteria for evidence and a not rare disease set of criteria for evidence. I know that makes it more complicated in one sense but in another sense it means we can remove this cut of common/rare as a reason to go to one level or the other. It does mean that we have to perhaps with some research think about what inherent limitations there are in the expectations for clinical validity data when a disease is rare. I think rare in that sense has got to be incidence-based.

DR. PENCHASZADEH: Following up on what Wylie was saying, I think that there is a case for keeping rare diseases in a separate category. I think we have to work out a little bit of a definition but I think it is essentially on the basis of making sure that tests will be available and that there will be no unintended barriers to developing tests.

I was thinking about this question of prevalence and incidence. Actually, it largely depends on the techniques you used to define a case because if you take, for instance, the case for cystic fibrosis, if you were to do at any point in time newborn screening, you would have essentially a prevalence at birth, which will be very similar to the incidence. That may not be applicable to late onset diseases or for disposition or predictive testing. I think we need something that may require a little bit of maneuvering with the official definition and see what is their proper criteria that one could set up to claim to the group of diseases because they are rare, require not lesser scrutiny but at least a different set of required information before a test is accepted for clinical use.

DR. CHARACHE: Using Wylie's concept of having different requirements for amount of data available at the time you review the test if it is a rare disease or a common entity. This is in line with what the Notice of Intent was after and the CLIA group. They actually spelled out a different number of kindreds in different types of samples that one would be thinking of for a rare disease versus a common one. That is how that was approached there and it would fit very well with that concept.

DR. KHOURY: Before you scratch this, I think what I heard Wylie say that maybe under 1 and 2, there is 1 rare, 1 common, 2 rare, and 2 common. So, I would like to make the suggestion, instead of complicating our life is to have 1, 2 and then rare because -- it is sort of 1, 2 and 3, instead of taxing that box, we make an early determination after the population criterion to classify bilaterally the condition and then funnel that to a separate process that borrows on elements of 1 and 2. We can define rare versus common. We will use something that this group will come up with based on research because otherwise it becomes 1(a) and 1(b) and 2(a) and 2(b) and then you would be complicating your life unnecessarily. So, I am making a case for 1, 2 and 3.

DR. MC CABE: Shall we have some discussion of that. Basically, what I am trying to do now is to get us to a point where someone, one of the staff can draw something

overnight that we can react to tomorrow. So, I am just forcing the discussion because I want to try and have something by the end of tomorrow that we can at least go and work on definition of rare, common or whatever, but I want to have something.

DR. PURYEAR: The way that Ed is doing it is it puts it in the context of the intended use, which I think is certainly easier for FDA, and that you have categories within that.

MR. HILLBACK: I think we have had the same problem for the last little while on the intended use as well because every test that Muin listed in the other version of this as Level 2 because of intended use started off life as a diagnostic test, which would have been Level 1. It happens that today because they have been out awhile, they are being used in a broader sense but when they came to the market the first time, whether it is a CF test or Gaucher's disease or Tay-Sachs, they came as -- I think most of them on that list if I am not mistaken came as a diagnostic test, not as broad public use.

So, I think we are going to have the same problem of the process at FDA is going to be to look at things the first time that way. I think it does get easier when you get to diagnostic versus predictive, some of the tests that we have all been talking about for a year and a half that initially are predictive in nature, but I think the intended use one is going to be just as hard to do as the size has proven to be.

DR. CHARACHE: I am really agreeing also with Elliott. I think everything is going to come in Level 1 if it is diagnostic versus predictive as the discriminator. I am also wondering from Muin why -- there were two things that I didn't catch that were on the original one, which was the medical and social implications and the availability of treatment or a reason to want the test.

DR. KHOURY: I guess in our infinite wisdom, we decided that this information may or may not be available and we said let's take the conservative view and say at the beginning of a pre-market analysis that if a test is going to be earmarked to healthy people at the time to predict the future risk of disease, let's consider them Level 2 until proven otherwise. Could be

part of the Level 2 analysis is to view all of these things inside the box. Is there significant social issues and then review those things. We thought that if we do it that way, then we can see as a maximum number of heads how many of the current 800 would fall into that box.

We found out that not too many really.

DR. CHARACHE: I am looking at the setting of precedence as well and the reason for separating genetic tests was because of the social and medical implications of that particular category of test. If all we are separating is diagnostic from predictive, it is going to apply to every test there is at the FDA. Am I right, Steve?

DR. LEWIS: I am beginning to wonder if we need two levels of scrutiny. I mean, I am hearing us say that either everything falls into Level 1 or everything falls into Level 2 and it depends on how you interpret things. I am wondering if we really two levels of scrutiny.

DR. MC CABE: I just want to come back to the concrete here. Certainly we can decide that we don't want to do anything and start all over again, but I would argue that that is just because we don't know how good or bad that model would be. Therefore, it would probably have the same problems as the one we have gotten to know well.

You have tried this one out, right, Muin? This is the one that you have tried out?

DR. KHOURY: Yes. I mean, you have the number of conditions that fall into it.

DR. MC CABE: And it was a relatively small number.

DR. KHOURY: Very small number.

DR. MC CABE: So that it is one that looks reasonable in terms of functionality for the FDA. If you look at it then, you have "yes" if it is population-based, "no," and if it is "no," then you look at diagnostic versus predictive. It separates out the diagnostic going to Level 1 and we have said all along that that was less concern to us. The concerns were the predictive and the population-based and those numbers are relatively small.

DR. KHOURY: But if you put the rare diseases in it, then you overwhelm -- most of the 800 will fall into Level 2 because as Pat or somebody said --

DR. MC CABE: But somebody made the argument and I can't remember who now, that the issue of rare versus common is really an issue of how much data do you need. Therefore, you may need different guidelines under both predictive and diagnostic for rare versus common in terms of the threshold that they would need to achieve regarding the data.

It is basically looking at perhaps not requiring the same power calculation for a rare disease versus a common disease.

DR. CHARACHE: But all of Muin's fell out the way they did started as a diagnostic. They are now in a different category but we are talking about the first review.

DR. MC CABE: I guess I have been reassured by the discussion today and learning more about the off-label use and the claims-based review that there would be some benefit. For people who are going to do population-based screening, there will be some value in getting that claim approved. There will be some economic value to doing this.

DR. COLLINS: I guess I am concerned that here is sort of late effort after a long day that we are perhaps backing away from some pretty important conclusions that we have reached over the course of more than a year and particularly that the working group put together at our last meeting and then we discussed as a whole.

What I hear happening is more and more people sort of backing away from trying to draw boundaries and saying, well, we will let the FDA decide within a particular level how they are going to handle this one or that one. They will be rare. They will be common. We will take these three criteria that we use to apply to predictive and we will assume that the FDA is going to apply those.

I am not comfortable with that. I think that is sort of skipping our charge a bit, that we were supposed to provide more guidance than that and we should try to do so. I am going to go back to what is up there and I actually think we are making a mistake if we take the

rare category and try to blend it in in some way with Level 1 and Level 2. I mean, the things that are going to change if you do that are as recently just been pointed out, it is a long list of rare conditions, which have the possibility of being used for predictive purposes but not on a population screen.

Instead of going to Level 1, those will now go to Level 2. That is, if Level 2 really does involve more effort on the part of the test developer, that is going to discourage those test developers for these rare conditions for going through this process at all. It just may not happen. If they do get to the trouble of going through it, it is going to put the FDA in a situation of being given a charge here to look at those tests with Level 2 scrutiny, which does imply a certain amount of additional close attention.

I thought we had it right before.

MR. HILLBACK: Would you put prevalence in front of intended use then, Francis?

DR. COLLINS: Yes. Before Ed put scratches on the diagram, I liked it okay, except I think we still have to wrestle with the predictive versus the diagnostic.

MR. HILLBACK: No, I am talking about the sequence because right now you kick out things that might be used for population-based -- Tay-Sachs and Gaucher's have small populations. So, wouldn't they be Level 1 because of that?

DR. COLLINS: Population-based testing, no. It ought to be Level 2. I thought the CDC did a good job of restructuring this except I am unhappy with the bottom category of predictive versus diagnostic, but otherwise I would be loath to take something that we really worked hard to come up with a solution for and throw it out based on arguments that are sort of being formulated late in the day when we all sort of tired.

DR. BURKE: I just want to briefly comment, too. I agree with what Francis just said. What I also want to say is I do not think every test will come in as diagnostic. I think there are tests that are predictive from the beginning. It depends upon how you define them. My

preferred definition would be a test that predicts a probability rather than a certainty of disease is always predictive, whether it is being done in asymptomatic person or not.

I just throw that out because I think we need to discuss that very possibly tomorrow if not today.

DR. MC CABE: How many will ever start as population-based?

DR. BURKE: Well, we have already said few, but some.

DR. PENCHASZADEH: I am really concerned actually about the question of intended use because, from what I hear, most tests will initially be marketed as diagnostic tests and I was not reassured by the comments from the FDA people that an eventual change in use based on experience and so on will really drive the developers back to the FDA.

I am really struggling with this because perhaps one should include something about potential users. If you have a diagnostic test with the potential it can be used as a predictive test or potentially can be used for population-based screening. From the very beginning you would fall into a higher scrutiny level.

The other issue, however, is that any population-based test most likely will always come from a policy decision of whoever is in charge of a population, the state or public health service, or based on standards of practice issue by professional organizations. That is actually a little bit in the other way of saying I feel more reassured that no matter what the developer of the test may want to do, there will always be a public policy level that will decide on the proper use of a test.

I just leave that on the table as a concern but I think we should be very conscious of the fact that -- I am sure the industry will find a way of initially marketing a test for the lower possible scrutiny level, which will be a diagnostic test.

DR. PURYEAR: I have a question actually to Steve. Before a test becomes diagnostic, it doesn't have to be proven to be diagnostic. So, not everything can come in as diagnostic because --

DR. GUTMAN: Well, it has to have a legitimate intended use and --

DR. PURYEAR: You can't just come in as diagnostic unless you are truly diagnostic. So, I don't think that is a worry that they are going to take the easy way out because they can't take the easy way out.

DR. PENCHASZADEH: How do you define diagnostic? I mean, if you find a mutation, you are making a diagnosis of the existence of a mutation and, of course, you will have --

DR. PURYEAR: Well, then that is as far as you can go. You can't say anything diagnostic about a condition. But the other thing is maybe we shouldn't call it level of scrutiny. It is sort of levels of review and then it is less pejorative sort of.

DR. KHOURY: Let me just step back and take some of the common sense approach to this, which is what we tried to do and maybe compare the public health view of the world with a pure regulatory approach and tried to meld these two together. I think this is what we tried to do.

There are instances, Victor, where there are manufacturers like a company that want to add supplemental newborn screening and they are selling that product as a population screen from the beginning. They were home brews and MCAD and LCHAD and the whole tandem mass spec. We want to capture these at the beginning as a public health agency, although the numbers of these is rather small and we hope that there will be developed through consensus development and task forces and sort of the PKU model or the sickle cell disease model, but there are instances and we are seeing them that are occurring today where straight off the bat people want to market newborn screening tests to the whole population. So, we want to capture that small part.

If we go to the rare versus common, if we don't do that, then the next level is going to complicate our lives. I would like to offer an addition to predictive. My view of diagnostic versus predictive has been guided by the idea that I want to scrutinize any test that is

given to a healthy individual who has no signs or symptoms at the time of testing for predicting the future risk of disease. I want to know whether that -- bilateral mastectomy, for example, is a harsh intervention in the face of a probabilistic test that gives you incomplete information. From a public health perspective, the APOE4s of the world and the BRCA-1s make it to that extent.

Also, the prenatal test, which I am not in any box right here. For me, I mean, prenatal testing carries all kinds of implications on the ethics side. So, whether we call them prenatal diagnostic or predictive, it doesn't compute in my mind. I put them in that box of higher level luck, review, to see if there is a buy in, sort of the karyotesting around CF type discussion. So, to me, I would add that in the bottom, sort of the prenatal diagnosis as a third category and the fourth would be pharmacogenomics. That is the big, big one, which is neither diagnostic nor predictive. It could be either/or, depending on how it is used. Some of the levels of scrutiny -- we need to discuss pharmacogenomics because we haven't really done that.

So, what I am advocating is two more boxes down at the bottom, sort of diagnostic, predictive, prenatal or preconception, whatever --

DR. MC CABE: What I have been hearing is PMD is a Level 2. Is that right? Or are people not sure of that? I have heard different discussions of that.

DR. BURKE: I think there is uncertainty about that at this point.

DR. MC CABE: What I would like to do -- we will always be left with some uncertainty. Maybe we don't get all the boxes in here and maybe we continue to talk about prenatal and pharmacogenomics. I would like to have something by the end of tomorrow to talk about.

I am out of order.

MR. HILLBACK: I guess I have two points. One is that I hear Muin, but on the other hand, if you have a family with two kids that already have Gaucher's disease and the third one has no symptoms but is three years old and you do a test, that is not predictive in the sense

that we should now move this over to some other category. I hope that is not what he is suggesting. That is just doing good practice.

But I think the bigger issue is that we have to be careful that we think of this in the sense of total clinical practice, not that it is what the labs do because the labs are not driving an awful lot of this. I think we keep coming back and I hear phrases that the labs are driving this, the labs are driving that. The labs don't drive a lot of this. It is the combined clinical practice that changes how a test is used. We can regulate the labs all we want, but that only is a little piece of it.

I am not arguing we tear this whole thing up, Francis. I really am not, but I think it is not as simple as to say we can just make these hard and fast rules. If the kid doesn't have symptoms, it is predictive. I don't think that makes sense. That is not how we work.

DR. MC CABE: We have fiddled with this a bit. Muin has actually tried it out and it works reasonably well in terms of not creating a bottleneck for us. What I was going to suggest, we have gotten into this issue of prevalence versus incidence. What you really did was you were looking at an incidence with the 10,000. We can very easily say a prevalence with a cutoff of 1 per 2,000 or an incidence with a cutoff of 1 per 10,000 and say either/or because for some diseases we will have better incidence data than we have prevalence data. That was going to be my suggestion as an addition to this figure.

DR. BURKE: Are we running out of time?

DR. MC CABE: Yes, we are.

MS. DAVIDSON: I was just going to come back and finally answer your question, Ed, about what I thought of the rare disease, 1 in 10,000 figure. I think it is something that needs to be looked at, but my sense at this point really is that I liked Muin's presentation when he talked about having a third category for non-population-based rare diseases, not only I think for the reason that you brought up, Wylie about needing a different level of documentation

to establish significance, but I think there are going to be some issues around rare disease tests over and above also the technical assistance that some laboratories, as well as groups, will need.

But even the issue -- I was just talking with some of my colleagues back here -- I think that the prenatal testing issue in the rare disease community is perhaps one that will have a different flavor. So, I would really argue for --

DR. MC CABE: So, you would argue for three?

MS. DAVIDSON: I am going to go back to Muin because Muin laid out some kind of third categorization.

DR. BURKE: I think actually the suggestion was that the first arrow pointing toward level 1, which goes from rare, that that would become Level R or whatever it is, a special level of scrutiny that has to do with rare diseases.

MS. DAVIDSON: The second issue is Michele's point, I think, is very good and I think we might want to think about the term "common," as well. We will have time I think after we get the model put together. But it needs to be presented in a way that the reader really understands that this is done in a thoughtful way for the populations that will be served.

Again, I want to come back to prenatal testing in general. I think this is an important issue and I would strongly argue that any tests that are used for prenatal decision-making, that they need a high level of scrutiny and that we need to give Level 2 strong consideration.

DR. BURKE: Even if they are rare diseases or are you still putting those in the R category?

MS. DAVIDSON: For all.

MS. BOLDT: I know it is very late but I am not convinced that we still don't want to use the box that we talked about from our original flow chart in terms of the intervention, unproven or not. When we talk about intended use, some of these issues are still applying to

diagnostic tests. Huntington's disease can be considered diagnostic. There is not a proven intervention.

Maybe we need to look at that box still. I just think we have ignored it and I am not convinced we shouldn't. We are talking about prenatal testing, that still has social and medical risks.

DR. BURKE: What do you think about time, Ed?

DR. MC CABE: Well, I think everybody is getting very tired. My purpose of getting up here was to focus and be sure we had something concrete. I think we need to discuss this tomorrow again, but all that I am getting is sort of a consensus change on this chart is to change this one Level 1 to a Level R. We can think about that and that then we talk about the issues that Ann raised. We can discuss those tomorrow.

[Whereupon, at 5:50 p.m., the meeting was recessed, to reconvene at 8:00 a.m., the following morning, Friday, November 3, 2000.]