SECRETARY'S ADVISORY COMMITTEE ON GENETIC TESTING

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Rockville, Maryland

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CONTENTS

Discussion of Oversight Issue 3

Appropriate Levels of Oversight for Categories and Data Collection, Evaluation, and Dissemination: Possible Approaches to Oversight Issue 4

Kate C. Beardsley

Data Collection Strategies in Genetic Testing: DHHS Public/Private Partnership Pilot Project

Muin Khoury, M.D., Ph.D.

Discussion of Oversight Issue 4

Discussion of Conceptual Questions Regarding Oversight Issues

Discussion/Approval of Draft Consultation Document and Outreach Mechanisms

Discussion of Other Issues

P R O C E E D I N G S (8:30 a.m.)

DR. McCABE: Good morning, everyone. Just a couple of announcements. First of all, there are handouts next door. They were out in the hallway yesterday, but with 300 people across the hall going into their meeting, we were afraid that any handouts would be picked up by that group by mistake. So they are next door in the overflow room if you need them.

The other thing is there is a sign up on the board for those of you members of the panel. You need to fill out your transportation form so that they can order cabs for us at the end of the day. My plan is that we will be over by 5:00. So that as you are making your travel arrangements, if you would take that into consideration.

Any other housekeeping things? Oh, yes, lunch. Because there are 300 people next door and they plan to break at 12:00, we are going to plan to break at 20 of 12:00 so that we can try and get everyone downstairs ahead of the group across the hall so that you can get your lunch. And we will give ourselves an hour, so we will just start a little earlier than we had planned.

Then let's get started for the morning. This morning we are going to look at the role of the states and the private organizations in oversight of genetic tests. We are extremely pleased to have a distinguished panel here. I will introduce them individually as they give a brief talk from the podium and then we should have time for panel discussion.

First of all is Dr. Ann Willey, who is Director of Laboratory Policy Development at the New York State Department of Health. She is also an associate professor of biomedical sciences at SUNY School of Public Health. Dr. Willey received here Ph.D. from the University of Minnesota and is currently pursuing a degree in law. She has a background in public health in genetics, and her authority in quality assurance is well-known and well-recognized by many of us in the field of genetics.

Dr. Willey?

DR. WILLEY: Thank you, Ed.

I used to say at meetings like this I'm from the government and I'm here to help. Now I can almost say I'm a lawyer and I'm here to help. And I am not sure which gets the worse response. I am going to speak very briefly about the history and how New York State has been involved in the oversight of laboratories, and then more specifically about our involvement in genetic testing labs.

Now being a student of law, I have recently concluded a legislative history of our authority over clinical laboratories. It actually dates back to the creation of the Department of Health in 1901, where the commissioner was given authority to enter into contracts and to specify the methods to be used by laboratories that performed those assays which were required under the Sanitary Code, things like bathing beaches, and food, and infectious diseases.

New York State issued its first approval of such laboratories in 1915. It was generally a voluntary program, although funding from the state and collegiality with the Health Department required such approval. And approval was granted on the basis of the credentials of the director.

In 1964, in response to the growing variety of assays that were being performed in clinical laboratories, particularly clinical chemistry and hematology, there were a series of studies which indicated that reproducibility of specimens from one laboratory to another was atrocious, and that false positives and false negatives that led to unnecessary therapy or the lack of appropriate therapy were rampant.

New York State passed legislation in 1964 which required clinical laboratories to participate in what was then a very rigorous, and remains today a very rigorous regulatory program. The program continues to be based on the credentialing of the director, the physical inspection of the laboratory, and proficiency testing challenges where appropriate and where technically possible.

We currently issue permits to well over 1,600 laboratories all over the world, because the New York State Public Health lab licensure bill is perhaps unique in that it requires laboratories testing specimens which originate in New York State, regardless of the location of the laboratory, to participate in the program. The program divides laboratory testing into a series of technical categories primarily for the efficiency of the program, not always for the efficiency of the operation of the laboratory, because we have to keep track of the methodologies and primarily the purpose for which some of these assays are being done, or the clinical validity and clinical utility, in the language of your documents.

Since 1972, we have issued permits to laboratories in a category called cytogenetics. Now, there is some debate today on what cytogenetics encompasses. As we move to molecular probes that are used in FISH technology, and when we move away from metaphase chromosomes to interphase detection of nucleic acid sequences, there is some debate as to whether that is cytogenetics or whether that is something else.

Since 1990, we have had a licensure category described as genetic testing. Our definition is slightly different than ones used by other task force and others in that it limits this category to testing for disease markers which are inherited. So they are germ-line mutations. We incorporate acquired mutations associated with neoplasia and prognosis and disease progression in a category described as molecular oncology. So, if you are doing DNA markers by PCR, by amplification, or whatever method, we divide it by the purpose of that assay, not by the method that is used.

We also have issued permits since 1990 to laboratories conducting genetic testing using biochemical assays. Many of these assays were in our system under clinical chemistry or hematology and there remains some difficulty in dividing them out. But we continue to, if you will, ferret them out and move them into a different category. Which only means we issue a piece of paper to the laboratory with a different lab category.

Genetic testing in New York State, we currently have 55 enrolled laboratories that hold permit in either biochemical or DNA-based genetic testing, or both. We have 10 what we call pending labs, laboratories that have applied but not yet received a permit from the State of New York.

I want to describe the process because I think it gets to some of the issues you describe. In applying for a permit, and this process applies across the board to all laboratories regardless of the type of testing, the purpose of their testing that they might wish to apply, the first step is the credentialing of the director.

Our statute requires that the director hold a doctoral degree and have four years post-doctoral clinical laboratory experience, and in categories of specialty such as genetics, cytogenetics, molecular oncology, two of those years must be in the specialty. Now these are not sequential years. None of us would live to be old enough to direct a major pathology laboratory. They can be concurrent, and we do look at letters of reference, transcripts, publications in determining the credentials. In genetics, we do look at American College of Medical Genetics or American Board accreditation, although that board, being a two-year board, is not sufficient in and of itself and is not a required credential, although it is of great value.

The second, a laboratory that has applied, filed all the paperwork, paid their $1,100, and accredited their director is put into applied status. The laboratory is then physically inspected to verify that this is a real lab, not a garage, not someone's office.

The third part for any laboratory is assessment of proficiency. New York State does not currently operate a genetic testing proficiency testing program, particularly because we have no common array or menu of assays to make the production of such a test feasible or reasonable at this time. The most common assays in our genetic testing labs are Fragile X, cystic fibrosis, and, you might be surprised to learn, Gaucher's disease by number of tests performed, not by number of labs offering the test. So it is conceivable you could pick CF or Fragile X but you would still not encompass all of the laboratories. And so we have looked at things like procedural PTs but have not put them in place. So we rely on the standard that requires a laboratory to assess its proficiency at least every six months -- sharing specimens, pulling specimens out of the freezer, having some means of assessing their proficiency.

The other aspect of the New York State licensure law is that it requires all methods used by any laboratory to be generally accepted by the scientific community, which usually translates into FDA approval of the methods and use, or the grandfathering of the methods and use, and/or acceptable to the department. This latter phrase has been interpreted to give the department a great deal of responsibility but a great deal of authority.

Probably starting with the category of genetic testing in 1990, we have required laboratories wishing to add such assays, since all of them are home-brewed, to submit technical validation. That includes the scientific basis of the test, including the literature if any exists other than their own; the actual method to be applied; the description of all reagents to be used including pre-analytical quality control on those reagents, and that gets to the issue of vendor-supplied research labelled reagents where the vendor's quality control is not sufficient; and the actual method to be used; the results obtained on known positives and negatives, and we could debate what a known positive is in some of these instances or what a known negative is for that matter.

And the numbers that have to be studied are, of course, constantly debated and we cannot provide a minimum number because it will depend on the population that is going to be studied and the prevalence of the disease in that population as to how many they are going to find. If we required ten positives, that might be more than the entire population in New York State affected with the condition.

They submit that data, their plan for periodic assessment, all of the documents that they use for marketing the test, all the requisition forms, the proposed report forms which have to include the interpretation, their means of obtaining clinical outcome data so that they are going to be able to go the next step at some point, clinical validation, and in New York State the consent documents are covered by civil rights law which require explicit consent and, although we don't enforce that law per se, we do look at compliance with that process.

This validation process would be followed for any laboratory adding any home-brewed assay in any category. It is not unique to genetics. What is unique to genetics is that some of these laboratories offer only genetic tests; many of them are academically based, have no experience with clinical laboratory protocols in terms of accession records, and recordkeeping, and personnel credentials, and we are more likely to have problems there than we are with the methods that are submitted. It is extremely time-consuming. At any given time, the staff responsible for review of these documents probably has a stack in their office often feet high waiting for review. We attempt to complete such reviews in a 30-day turnaround time.

Now, obviously, there are laboratories which offer unique genetic tests who are not part of the

New York State system because they have no major New York clientele, and if it is a unique assay and unique disease, they are the only lab in the world, they are not going to be participating. We do have a process by which such laboratories can receive a restricted permit on a patient-by-patient medical necessity basis where the referring laboratory, which under the statute, if they hold a New York State permit, cannot use any other lab that does not hold a New York State permit unless they seek the approval of the department, makes such a request specifying the medical need, the laboratory to be used.

We generally issue those approvals really without review of the credentials of such a laboratory with the specification that the patient be informed that this is being done outside of the quality assurance program in the State of New York, and that results may never be returned because a laboratory labelling itself as a research lab may have no intention of releasing clinical results. And this is something that needs to be very clear up front.

So we do have a system that started with genetic testing, it applies to all labs for any assay, for any category. So we get a lot of requests for holistic medicine and some very bizarre assays as well. The system works very well although it affects only labs doing business with New York State, and I have the list of labs with me. I have copies of my regs with me. If anybody has any questions, I will be happy to answer them later.

Dr. Howell is going to speak next. He reminded me of something in the hall, I realize my mind sometimes is on other things, he asked me what I knew about the joint project with the American College of Medical Genetics. I denied knowledge and I shouldn't have. I have read the document a million times. In talking about partnership arrangements, New York State, through its Office of Quality Improvement, put out a contract or a grant opportunity to professional organizations to draft clinical practice guidelines in a variety of areas. Two were related to genetics; one was breast cancer screening, and the other was the assessment of childhood multiple congenital anomalies.

The grant was issued to the American College and joint activities were pursued over almost three years, with a clinical practice guideline very recently having been distributed. I commented that it gave very little detail to laboratory issues because, of course, in New York laboratories are presumed to be, if you will, under control, and as a New York document there is not a lot in that document about how to regulate labs. But we will hear from the College then.

Ed, thanks.

DR. McCABE: Thank you.

Our next speaker is Dr. Rod Howell. Dr. Howell is currently the president of the American College of Medical Genetics. He is also a professor and chairman of the Department of Pediatrics at the University of Miami School of Medicine, and Pediatrician-in-Chief at Jackson Memorial Hospital. He received his M.D. from Duke University. He is the author of over 150 articles and books, has membership in 16 professional societies, and has been on the faculty at the Johns Hopkins University School of Medicine, the University of Texas Health Science Center at Houston, and Baylor College of Medicine. In addition to serving as president of the College, he is also chairman of the Research and Review Committee for the American Board of Pediatrics, and a member of the House of Delegates for the AMA where he represents genetics.

Dr. Howell.

DR. HOWELL: Thanks very much, Ed.

As most of you know, I presented a fair amount of material yesterday about some of the activities of the College. Today, I would like to focus on just a few things that I would like to see the committee keep on its plate as it proceeds. I am going to speak briefly about education again, because genetic testing is unique in that education is a key part of the process.

As I look at the problems before us, the regulation and assessment of quality in the laboratories is well underway and there are many programs of the kind Ann talked about, some under CLIA, some in conjunction with CAP, other professional organizations in the College that are really defining I think quite worthwhile guidelines for the laboratories. But the problem is genetic testing is it is essential that the person requesting the test and the person receiving the results be educated about what that test does. And that I think is one of the very big issues in the whole genetic testing area.

The College is very active in this area in a variety of areas. One of the more interesting ones is that we have recently had discussions with a considerable group of national private laboratories about the prospect of developing genetic educational material that they might utilize when people are requesting tests from the commercial laboratories. We think that is a great opportunity and a great partnership.

I think the question that I would like to address is the big issue I think has to do with predictive genetic testing, and you can look at this in a variety of ways. But I think the application of a genetic test to a patient with cystic fibrosis or a malignancy, I think for the laboratories there are already mechanisms under which the quality of their testing can be regulated and assessed. And I think they are improving all the time. The groups are working together. CLIA is increasingly working in the area of genetics and improving its ability. So I think the laboratory tests in those areas are fairly clear, and I think that the application of those tests falls largely in the area of the practice of medicine.

I think the question is, how does one gain oversight then as you move forward into this huge number of genetic conditions that have a predictive nature? And I think that oversight should be a public-private venture. And as I think of models for that, there are three groups, organizations, activities with which I personally have had experience that I think might be useful models, at least parts of them.

It has already been mentioned, and I will not belabor this, the cancer model, but I would like to elaborate on that a little bit and move back to the pediatric model of cancer and the pediatric oncology groups, of which there are two, soon to be one. But for instance, at the current time, over 90 percent of all the children in the United States who have a malignancy are treated under the protocols of the pediatric oncology groups, and, again, these have been organized through the federal government, through the local universities, the local laboratories. But they basically are quality assurance programs.

There are protocols so that the patients are entered into the system, their disease conditions are assessed as they go along, new treatments are introduced, et. cetera. But there is a whole array of activities going on in these. I might point out all patients who are enrolled in these have a very extensive informed consent at the time of enrollment. So they are fully aware of the fact that they are enrolled.

And those of you who have had a child or a relative with a child who has a malignancy in the United States, the chances are overwhelming that that child has been a part of these programs. They have been very effective and have involved coordination with virtually everybody you can think of.

The second group is a more research oriented thing that has to do with the neonatal intensive care units. As you know, neonatology has advanced probably as rapidly as we hope genetics will in the past 20 years with various technology. But there are currently 14 large nurseries in the United States that operate a consortium. They have been in business for more than ten years. I think the primary funder is NICHD.

But, fundamentally, there is a national series of protocols that are applied in these nurseries so when a new technology appears in the literature, a writing group will get together, develop a protocol for assessing this technology, it will be tried in a series of places with constant assessments, with good data acquisition, et. cetera, and outcome data, and it will soon be apparent whether or not this is a worthwhile treatment, et. cetera. But these nurseries have been very, very good.

Now the other thing I would like to speak about ever so briefly that I think has even more relevance is the collaborative PKU project. And, again, this has been talked about a little bit. This is the most widely applied genetic test in the United States, because all babies born in the United States currently are tested for phenylketonuria without exception. But when PKU was initially identified over 30 years ago as a treatable disorder, the screening test was rapidly deployed throughout the country because it was perfectly apparent that many children who had high level of phenylalanine, if you restricted the diet, would benefit dramatically.

So what happened was the NIH formed the collaborative program for the treatment of phenylketonuria and major centers around the country got together. There were a huge series of issues that were looked at -- the diagnosis, the laboratory testing, the clinical outcomes of these patients. In other words, what happened, who needed treatment, who did not need treatment, what was the proper level of phenylalanine to be maintained. At the beginning of these projects, none of these were known. But over the past 25 years, phenylketonuria has been well-defined. There have been patients who have been identified that benefit greatly from treatment, others that are complicated, et. cetera.

But again a public-private collaboration that has involved the clinical laboratory system, the public health system has been extremely widely involved in this as far as quality control, the professional groups such as the American College of Medical Genetics, CAP, et. cetera. I think that if you look at oversight, obviously laboratories are going to need to be controlled carefully, as they are now, as far as quality assurance and requirements and so forth. But I think the collaborative prospective mechanism to do genetic testing, to evaluate the results, to look at protocols and so forth with an ever-changing program, in other words, none of these programs can be static because new information comes out weekly, and again education, et. cetera, can all be built into this.

And so I think that looking at a public-private thing, I know Muin is going to talk further about this today because there has been a lot of discussion in regard to cystic fibrosis and certain other conditions. But those are some of the thoughts that are on my mind as we come up to this morning. I might point out yesterday I was not very kind talking about physicians and their education in genetics, which needs a lot to be done for it. I also was not kind to the regulatory bodies. But for those of you who have read the U.S. News and World Report article, I would like to add that we also need to urgently get the press better informed about medicine and genetics.

DR. McCABE: Thank you.

Under Tab 9 is the information from the American College of Medical Genetics. It includes the standards and guidelines for clinical genetics laboratories from the College.

Our next speaker is Dr. Walter Noll, who is a member of the College of American Pathologists Molecular Pathology Committee and the CAP-ACMG Joint Committee on Biochemical and Molecular Resource. Dr. Noll is a professor of pathology at Dartmouth Medical School and director of clinical chemistry and molecular genetic diagnostic laboratories at the Dartmouth Hitchcock Medical Center. He is a founding member of the College of America Pathologists Molecular Pathology Resource Committee, and a founding member and immediate past president of the CAP-American College of Medical Genetics

Biochemical and Molecular Genetics Resource Committee. He is also a member of the Molecular and Clinical Genetics Devices Panel of the FDA's Medical Devices Advisory Committee. Dr. Noll's research interests include familial cancer syndromes, and the application of molecular genetic techniques to laboratory diagnostics.

Dr. Noll told me he had prepared a 30-minute talk but has graciously trimmed it down to 10 minutes. Thank you.

Dr. Noll?

DR. NOLL: Thanks, Ed.

My job is to describe the College of American Pathologists programs in quality assurance. As I told Ed, this is easy for me to do I think in 30 minutes, to do it in 10 minutes is extremely difficult. So please refer to this published statement that we have prepared for you because I can't touch on all of these things.

We frequently speak about the quality assurance programs of the CAP as being in two parts: One is called the Laboratory Accreditation Program, which is an on-site inspection program of laboratories; and the second part is a series of proficiency tests, actually there are greater than 100 of these. But really this is one integrated program. One can subscribe to the proficiency testing surveys by themselves. But if one is enrolled in the Laboratory Accreditation Program, then one must also subscribe to the proficiency testing surveys.

Well how is this organized? Well, there are really three main components to these quality assurance programs. First of all, there of course must be a staff to articulate this and get it done.

Secondly, there is something that is known as the Commission on Laboratory Accreditation, which consists of 13 regional commissioners and under them a lot of state commissioners. What these people do is they deal really with the administrative matters of running the program. They deal with issues such as what should the inspection include; how shall all this information be documented; is this in compliance with federal, state, and private regulatory agencies such as HCFA, the Joint Commission; what action should be taken if a lab isn't up to par; who shall be inspectors and how should these inspectors be trained.

And then finally, and I am going to go into more detail about this, the real scientific core and expertise of both the inspection program and of the proficiency testing programs is really located in the scientific resource committees, and there are 30 of these. These people are the ones who design the checklist for the inspections, and they design, monitor, evaluate, they do everything that is involved in running the proficiency testing programs.

Some points to stress. First of all, this program is 50 years old so it is really very experienced. The program is also very good. And I think that is underscored by the fact that it does have deemed status by the Joint Commission, by HCFA, by some state agencies, and by the Department of Defense, Department of Veterans Affairs. The professionals who run this program, and these are the inspectors and members of the resource committee they're an enormous pool of volunteers. They all contribute their time, their ideas, and their abilities. Their intent really is to make this program good and to improve it. The program is also very large; 6,000 laboratories are enrolled in the accreditation program. That means that there are 3,000 inspections every year since on-site inspections occur on a bi-annual basis. And there are actually 25,000 laboratories which are enrolled in the proficiency testing surveys.

Let me tell you what a typical inspection process is. What happens is that the regional commissioner gets on the telephone and finds a team leader. This is an experienced individual who has done inspections before and assumes the role of team leader.

The team leader assembles an inspection team. At Dartmouth, if we go out to inspect a laboratory comparable to our own, this is typically 15 people or more. These people are pathologists, they are supervisory laboratory people, and they are other doctoral scientists. The inspection team receives an enormous amount of material about the lab that is to be inspected, including the results of the previous inspection and a fat stack of checklists which are used to actually conduct the inspection. Any bureaucrat would go into fits of ecstacy if he or she saw this wonderful stack of paper that we have to deal with. The team conducts the inspection, that usually takes a day.

At the end of the inspection, there is something called a summation conference where the inspection team presents its findings to the inspected laboratory. Generally, all of the personnel in the laboratory gather for this. There is an interchange then which is supposed to educate the laboratory, it is supposed to educate the inspectors. The team leader writes a report, that report is evaluated, the inspected lab then responds to deficiencies, then that is evaluated again, and, if everything goes well, then that laboratory is accredited.

I brought examples of the molecular pathology checklist. This is one of 12 or more of these things. It is big, it is extremely comprehensive, it asks very detailed questions. And as you might expect, it gets very heavily into the analytical part of doing genetic testing. This is the molecular pathology checklist. But what I do want to point out to you, because I know you are very concerned about this, it doesn't just deal with the analytical phase of testing. It also has some very pointed references to the pre-analytical and the post-analytical phases as well. I would like to just read a couple of these to you quickly.

For example, when the question comes up should this genetic test actually be done, there is a specific question that gets at that, and it reads as the following: "Are there written criteria for questioning or rejection of clinically inappropriate test requests?" Now this is a very short statement. And it is time for me to point out that for every question on this checklist, which is short, there is also another document. For each question there is something called a commentary and that commentary explains in detail what the intent of the question is, and that commentary is available to the laboratory and also to the inspector.

Let me just take a stab at what it says in the commentary for this very brief question. It says: "Many of the recently discovered disease genes subject to molecular genetic testing are extremely complex as to their size, mutational heterogeneity, penetrance, and expressivity. Especially with regard to presymptomatic testing, application of these tests to patients not carefully screened and counseled can be meaningless or damaging. For certain tests, only those patients with strict family history are eligible. There are also many ethical considerations, such as the policy of not offering predictive genetic tests to children unless there is a viable clinical intervention to be initiated." And it goes on and on. And it says here, "The laboratory therefore should have established guidelines for the rejection or questioning of test requests felt to be inappropriate on clinical or ethical grounds." Now this is something the laboratory must do to pass the inspection.

Then there is the analytical phase, of course, and then there is the post-analytical phase which for the laboratory really is the report. Let me just get at some of the questions that are directed at what a report must include, and there are several of these. I will leave this with Sarah Carr. I will read just a couple.

The first: "Are molecular genetic test reports released and transmitted in a manner adequate to maintain patient confidentiality at a level appropriate for the particular test?" Let me just read what it says here, if I can find it. "In view of the recognized risks of genetic discrimination and stigmatization, confidentiality of molecular genetic test results is an important consideration. Results should be communicated only to the referring physician, genetic counsellor, or in some cases the patient. A non-confidential media, such as a Fax machine, should be used with caution. Some patients aware of the insurability risk will choose to pay for testing out of pocket and request that the results not be recorded in their medical record. Such requests should be honored. Under no circumstances should results be provided to outside parties," et. cetera, et. cetera. And "The information should not be passed on to family members without the patient's expressed consent. Laboratory workers must even use caution when publishing or publicly presenting the results of studies such as pedigrees," et. cetera, et. cetera.

So, very heavily into the confidentiality issue.

A second question. "In genetic testing for complex disease gene with multiple possible mutations, does the report include an estimate of residual risk of being a carrier for one of the mutations not tested for?"

The commentary. "Many recently identified disease genes, such as those for cystic fibrosis and familial breast ovarian cancer, are extremely heterogeneous at the molecular level with hundreds of different mutations reported in different patients and families. Short of sequencing the entire gene, it may be impractical or impossible to test for every rare mutation. A negative test result therefore does not completely rule out the possibility that the patient is a mutation carrier. The test report must convey this information in a fashion understandable to the referring physician and, when appropriate, the patient. Whenever possible, a calculated value for residual risk based upon the known population allele frequencies should be included."

So it is highly detailed, quite specific, and I think quite comprehensive. And you must do these things.

Well, that's the on-site inspection checklist.

Let me now talk a little bit about the quality assurance programs. And remember, that is a part of the accreditation program as well.

The example that I am going to use is, of course, the molecular genetic survey or proficiency testing program because this gets at what we here are most interested in. I think I really would like to show -- do I still have some time?

DR. McCABE: Yes.

DR. NOLL: I will do this briefly then without projecting.

The molecular genetics survey is jointly sponsored and equally sponsored by the ACMG and the CAP. It is designed, monitored, and evaluated by a resource committee called the Biochemical and Molecular Genetics Resource Committee which also writes the checklist for the inspections. It is composed of six members from each society -- six pathologists, six people from the ACMG. It is really some of the best people that both of these societies can supply. I think Dr. McCabe, who is a former member of this committee, will support me on that.

The pathologists, in addition to being board certified pathologists, five of these six pathologists have, in fact, board certification by the American Board of Medical Genetics in diagnostic and molecular

genetics. There is a liaison member from the American Association for Clinical Chemists, which happens to be Dr. Altmiller, and there is informal representation from AMP, NCCLS, NIST, and the FDA.

One thing I do definitely want to show you before I quit, and that is the way this program has grown over the years since it started in 1995. There are two challenges per year if you subscribe to this survey. They are labelled the A and the B challenges. What you can see from the figure there, when we started in 1995 we were testing for four diseases; in the A challenge we tested for two diseases, in the B challenge we tested for three. You can see than now in the year 2000 coming up, we are now at a total of 15 different diseases, and for more than half of them they are challenged twice. Each of these challenges consist of multiple DNA samples and the laboratory must test for all of these.

I would just like to make a concluding remark. This program of course is very much in progress. It is something that is under constant development. I think we have our best people in the genetics and in the pathology communities directing a lot of energy at this. And I can also tell you in a preliminary kind of way that the College of American Pathologists has right now working its way up to the board of directors, and the board should get this by the end of the year, a very serious and aggressive proposal for increasing the investment of the CAP in these types of programs and in educational programs. I expect that is going to be a success. It will allow us really to I think triple our resources that we are able to put into this now. Thank you very much.

DR. McCABE: Thank you very much.

Our next speaker and final speaker for the panel is Dr. Dale Altmiller, who is NCCLS assistant chairperson for the Area Committee on Molecular Methods, and Chairperson of the Subcommittee on Molecular Genetics. Dr. Altmiller is a clinical associate professor in the Department of Pathology at the University of Oklahoma Health Sciences Center. He received his Ph.D. from the University of Texas in biochemistry and genetics. Dr. Altmiller's research interests include general and medical genetics, including the development of laboratory analytical methods.

Dr. Altmiller?

DR. ALTMILLER: Good morning. I am going to try to do my presentation backwards and try to subtract ten minutes off the time so that we can get back on schedule. Maybe that will work.

Since a lot of the attendees may not be familiar with NCCLS as an organization, I would like to make a few comments about NCCLS.

PARTICIPANT: Could you define the acronym NCCLS? Some of us don't know what that stands for.

DR. McCABE: I was going to mention there is a Tab 10 on the --

DR. ALTMILLER: NCCLS is no longer -- well, I guess you could say it's an acronym, but it stems from National Committee for Clinical Laboratory Standards. It used to be known as the National Committee for Clinical Laboratory Standards. The full name is no longer used. It is officially now NCCLS. So you can either call that its name or you can call it an acronym for the old name.

NCCLS is well-known to laboratorians. It has been in existence now for just about 30 years. It came into existence because of a need for standardization in the clinical laboratory. Clinicians and laboratory workers representing about 15 organizations came together about 30 years ago with the purpose of wanting to create something that would not be a government agency that would have as its primary mission to improve laboratory testing. And NCCLS sprang out of that initial effort.

I would like to give you just a visual overview of some points and then come back and make a few comments. NCCLS is now in the business of developing standards and guidelines for genetic testing. So that is the reason we are here today talking about NCCLS and what they might have to offer.

The main part of this that I would like for you to focus on would be the board of directors and the chairholders council, and then, below that, the area committees and the subcommittees. NCCLS operates with volunteers at the level of chairholders council, area committees, subcommittees, the working groups. There is a staff of approximately 26 people that is growing to take care of all the administrative and behind the scenes work, editorial work for documents and so forth.

The area committees are made up of volunteers. They receive recommendations for the development of standards and guidelines for laboratory procedures, for products also. The composition of area committees, as well as subcommittees, includes professionals from the laboratory disciplines, government, and industry. There is a strong attempt to try to keep this in balance, and there is a very strong attempt to eliminate conflict of interest. This is always at the forefront. Everybody knows who everybody else is representing.

The area committees are made up of members with voting rights, and then advisors and observers, a staff liaison to help in the administrative work of the area committee. There are some individuals here I know that are on the list of advisors and observers.

Dr. Charache is an advisor, is that correct?

DR. CHARACHE: Yes.

DR. ALTMILLER: The area committee identifies and prioritizes projects within each area, oversees developmental activities of its subcommittees, and actually creates the subcommittees depending upon the needs for guidelines and standards. Then when a subcommittee is actually formed, it is usually formed actually for the purpose of creating a guideline or a standard. Again, the composition would have representation from government, from industry, and from laboratory professionals.

You can see at the bottom we have this area committee on molecular methods. There are a number of others. One of the things I would like to point out is the way in which guidelines and standards actually get developed. And it is through the NCCLS consensus process. This process is open to all organizations in health care. It is balanced by representatives from the three areas that I have already mentioned. Fairness is given to consideration of all views and precludes conflicts of interest. The development is voluntary and the implementation is voluntary.

The consensus process has implicit within it there is a reiteration of the individuals making up the subcommittee, the writing subcommittee, that will bring their collective expertise on a subject that is being addressed, perhaps a guideline or perhaps a standard. The document will be developed and will be approved by the subcommittee at some point, will be approved by a board of directors at some point, and then will be considered a proposed document.

It would then be distributed to workers in the field, all member organizations It will go through a phase of review, and comments will then come back to NCCLS and be compiled. The subcommittee will then address all comments that are made of substance. Some are editorial comments and those corrections are made, if they are agreed with. And substantive comments are addressed and then are included in the next version of the document.

So the standard development involves volunteers, area committees, subcommittees, and the staff working together. NCCLS now has a lot of these in electronic products. And that is sort of the next phase of NCCLS is to be able to speed up the process at which standards and guidelines can be developed. In areas such as genetics, the technology is moving so rapidly that it stays ahead of us. And so NCCLS is complying with the new requirements of being able to develop guidelines and documents using electronic media through the internet so that both the development of the document itself and the comments coming back can be done and handled in a much more expedient way.

The electronic communications has as its objective to accelerate the standard development process, and to facilitate global input. This is another objective of NCCLS is to become more globalized in its influence. It is collaborating with the World Health Organization in this effort.

This is a composition of the NCCLS Area Committee on Molecular Methods.

These are some of the NCCLS documents that have to do with genetic and/or other areas using molecular methods. The first document that you see here, MMIA, Molecular Diagnostic Methods for Genetic Disease, is a document that will be published by the end of this year or in January of the year 2000 as an approved document. This document was put together by the subcommittee that I have chaired dealing with molecular methods for inherited genetic disorders. So we are not dealing with acquired mutations, but only inherited mutations.

This is a list of some of the others. Because of time, you can see they deal with cytogenetics, a new proposed project will deal with measurement and interpretation of trinucleotide repeats.

This is the composition of the subcommittee that prepared the document on genetic testing. That document has as its purpose to provide guidance for the use of molecular methods for clinical detection of heritable mutations associated with genetic disease.

We have dealt with these various topics: Nomenclature for designation of mutations, pre-analytical and analytical information, and laboratory results reporting post-analytical information. The focus of the document is more on the technology of genetic testing. However, there have been many precautions placed within this document that do deal with privacy and confidentiality and other ethical issues dealing with genetic testing. This is probably the first document that NCCLS has published in which there has been this much focus on ethical issues in testing of any kind.

In looking to the future, NCCLS, to meet the new requirements for genetic testing, is planning to meet in conjunction with the American College of Medical Genetics, the American Society of Human Genetics, the Association for Molecular Pathology, and is seeking global input for consensus development process.

The committee has in your packet the strategic plan for NCCLS and one of the catalogues. The strategic plan describes what is a consensus standard. There is not quite enough time this morning to go through and define in detail all the terms that are used. I would like to emphasize though the consensus process is at the heart of developing the guidelines and the standards.

Now I have not distinguished between guidelines and standards. It is almost self-explanatory but not quite. A standard is a document that a laboratory, if it adopts it, must use unchanged and verbatim. A guideline would have language such as "should." It contains recommendations that a laboratory can adopt and can actually make changes to if they wish.

Some of the documents that have been developed and approved by NCCLS are also adopted and approved by other organizations, such as CAP in its Laboratory Accreditation Program. And then those

documents are recommended to the constituencies of CAP who use the Laboratory Accreditation Program as good documents to use for getting their laboratory accredited.

This strategic plan describes how projects are chosen. That is, there is a selection of topics for which guidelines and standards should develop; how the consensus document is developed; and what are the benefits to health professionals, the benefits to government, there is a tremendous benefit to industry. Industry looks to NCCLS to develop guidelines before they really start developing a product. Once they know that there is an NCCLS guideline or standard in place, then they know that they can move ahead and pretty much meet the requirements, then it will assist them in going to the government agency for approval of their product.

So I will have to stop at that point.

DR. McCABE: Thank you very much.

At this time, we are going to have a discussion with the panel. Our purpose really is to talk about these various approaches that we have heard about to try to seek guidance on how we might construct recommendations.

Yes, Dr. Burke?

DR. BURKE: I have a question for Dr. Noll, and it has to do with the CAP criteria for rejecting a sample. If I understood, there would be certain circumstances -- and the sample should be used only in terms of certain family history, or if pretest counselling had been provided, et. cetera. My question is, do you have data on the experience of labs with rejecting samples? Can you tell us anything about how effectively that process is actually accomplished and what proportion of samples labs do end up rejecting? And what kind of resources are required to follow through with implementation of those written guidelines?

DR. NOLL: No.

DR. McCABE: Yes, Pat?

MS. BARR: I guess I have a question for all three of you. I was struck with the labor intensity of what you are doing, which is very commendable, but I am also struck with the expectation of significantly increased volume. So, while you said you were now doing a certain number of tests, Dr. Noll, if we imagine that there are now next year not going to be six diseases, but there are going to be 45 diseases, do you have a sense of the resources needed, the capability of your organization to deal with that? And I would ask the other two gentlemen the same questions.

DR. NOLL: That's a very important point. And I certainly am one of the vocal people in the CAP organization who is trying to make exactly that point. That is why I ended my presentation with the optimism that something really was going to happen.

My own personal view, and I think it is shared by my colleagues on the committee as well, is that it is going to explode. And for an effective proficiency testing program we need more diseases, we need more challenges, they ought to come more frequently, there ought to be more specimens. And there really aren't the resources to do that right now.

Why am I optimistic? The reason I am optimistic is because the CAP has actually gotten over a rather large hurdle in its computer system, for example. It was a very important hurdle. It sounds trivial

in a way, but it is extremely important. And what it is moving towards, and I think this will move along fairly quickly now, is to a menu-driven kind of program where laboratories can actually subscribe to the diseases that they are actually doing.

Automatically this will compress the cost, for example, because right now, if you are going to subscribe to the program, you subscribe for everything that is in the program even though you might only do a handful of these things. Because it will lower the cost, it will allow us to send out more challenges to individuals who are doing, let's say, cystic fibrosis testing, so they get lots of challenges rather than very few.

So how is this going to happen? A major recommendation has been made to the board to substantially increase professional staff support, this is doctoral level staff support in the College. Right now, we run on volunteer power. Volunteers are excellent with ideas, enthusiasm, energy to get things going. But when they go home from the committee meeting, they come back to all the work that they have left behind, and what they have done at the committee, everything they want to do sort of gets to the bottom. So what we need is people to articulate these things in a management kind of sense. I think we are going to get the doctoral level people to do that.

And the other component of that is a very substantial investment in education, which I think is critical. I think this is really the most important thing.

DR. McCABE: I'd like to point out that of the four presenters that we heard, three of these are driven by volunteers. And that is getting more and more difficult given the constraints on our faculty to earn their salaries. When people leave, as a department chairman, I am well aware of this, that when people leave and do the volunteer work, they aren't making their salary at home. And there is more and more concern about this.

Maybe Ann could comment since she represents the one group that isn't voluntary.

DR. WILLEY: And I think, as I commented on the manpower issues, I think resources for oversight of laboratories is something that seriously has to be grappled with. The New York State model is significantly different than the CLIA model. CLIA builds laboratories for the participation and issuance of certification by CLIA on the basis of volume, and they are categorized, and it is capped. New York State's licensure fee is not capped, it is a percentage of revenue. It is an annual calculation which takes the total cost of program last year, takes the total revenue of the regulated industry, that is New York State specimens tested in any lab in the country, divides our cost by their revenue and comes up with a percentage. Right now it is about 0.005 percent. We are talking on a percentage basis a very small number.

However, that means that the large national reference laboratories pay the State of New York approximately $1 million apiece for the privilege of doing business in the State of New York. Now, the New York State business base is $500 million to $1 billion each. So these are small percentages but large dollars. The median fee paid by a laboratory is something around $2,000. So that means we have a lot of very small laboratories. And genetic testing labs, if they are small niche single-disease laboratories who may not even be charging at cost, they may be recovering something, are not the big contributors.

Currently, the genetics initiative alone in the program, to hire the staff, to have the doctoral level staff to review the validation documents, to have people familiar with genetic applications from clinical patients all the way through to bench level labs, was $1.5 million out of a $15 million program. So we are currently committing approximately 10 percent of the budget of the program to developing manpower capacity in genetics. And as I said, that doesn't include proficiency testing samples. So that a

commitment to the oversight of such a program is very expensive.

I would make one comment about PT, though. We need to look at the model of clinical chemistry. No PT program tests every analyte that a clinical chemistry lab performs; there is some array. Under CLIA, it is a specified array, under many other programs it is a rolling array. I suspect that at some point in genetics we have to go to those things which are common, those methodologies which underlie many technologies.

And then, a motto that my staff has on the wall, "trust, then verify." We have to leave the labs to set up these biannual, or more frequent, it could be every month, it could be every week, whatever quality control protocol they put in place to assess their performance. And then it has to be monitored periodically; did they do what their own methods say they must do. Because as the array particularly in genetics is infinite, as some would suggest, we will never have challenges for every analyte.

DR. McCABE: Reed, and then Barbara, then Francis.

DR. TUCKSON: First of all, I am, on the one hand, very encouraged that all of you know each other and there are all these interrelationships that exist. Where I am confused is I am not sure I understand -- I am naive to this field and it is hard to follow it all. If I think about CLIA and what it does at the national level, then we have got the state level, then we have got volunteers in two different organizations, both of whom are interconnected at some level. Is this a system that works?

Are you saying to us that it ain't broke, don't fix it except for let's get some more money in it and you guys will handle this? Or are you saying to us that, as we look at this enormous expansion in the future not only in terms of volume, but also as we look at it in terms of the need to move from where we are now to predictive testing with all the new range of variables that must occur -- exactly what are you telling us, and what do you want us to do?

DR. McCABE: Do you want to --

DR. HOWELL: Dr. Charache has a comment.

DR. CHARACHE: I think that we will address this also in my presentation. I think you will see the overlap and coordination perhaps a bit there as well.

DR. HOWELL: Let me comment very briefly. We do all know each other. I think that at least the College's relationships with the various groups has been very fruitful. And I think to a considerable extent it isn't broken. But I think that there are clearly pathways to expand the capability that Dr. Noll has addressed very clearly. But I think that a critical issue has already been alluded to, and that is that the professional genetic component of this has been volunteer. That is going to be an issue that is clearly going to need to be addressed as in other areas.

DR. McCABE: Dale?

DR. ALTMILLER: Well, on the one hand, when you do notice that we all know each other, it may seem like it's kind of a good ol' boy system where everybody is working here in small groups of people. But actually, the consensus process is open and utilizes input from all sources that are interested. So in the NCCLS consensus process, it really does work. So that you end up with products in the form of guidelines or other products that are not necessarily agreed upon by 100 percent of all of the participants, but there is substantial agreement by all of the participants that this is the best available guideline or standard that we all can agree upon in principle.

DR. TUCKSON: And I know we're going to have other questions and discussion. I guess ultimately at some point, I don't know what the mechanism will be, but I think at some point we are charged with thinking about the role of the private sector versus the public sector here, and do we want government to come in and do this, what is the right role of government, what is the right role of the professional societies, the states, and so forth and so on. I think as we try to explore these questions, if at the end of the day you all were able to come back and sort of, depending on how the questions come, and give a consensus or recommendations that tell us how everybody sees this thing coming together, it might be more useful ultimately for the paper than the individual presentations.

DR. McCABE: Barbara?

DR. KOENIG: Well I think Pat and Reed have addressed the two main concerns that I had, the first being the issue of volunteerism in this field. And perhaps I am feeling it more acutely being in California where we are sort of on the cusp of the effects of the managed care revolution in terms of the impact on physician reimbursement and time for volunteer activities, so I can tell you that it is an increasing problem to get people to volunteer for anything or to come out for any kind of meeting. So this is I think a real issue in the future.

And then I had the same concerns about coordination among this number of groups doing voluntary oversight. So I agree with Reed that it would be very nice to have some elaboration of how this actually works out in practice.

But I did have another specific question about the issue, especially Dr. Willey, you mentioned, everyone mentioned increasing attention to privacy and confidentiality issues and pre- and post-analytic phases of testing. But can you give me a sense of what that phase of your process actually looks like. You said that you actually review informed consent documents. How does that actually work? And perhaps the others can address that question as well.

DR. WILLEY: The New York State legislature in 1996 placed within the civil rights law and human rights law, which is executive law in New York State so it does not belong to a particular agency, confidentiality in genetic testing legislation, which has basically two parts. One is explicit informed consent, which requires that the tested individual, whether this be paternity testing, DNA profiles, chromosome studies, or DNA-based biochemical genetic testing, be fully informed of the purpose of the test -- the test to be performed, the limitations of the test, associated economic potential impacts, the issues of confidentiality and who should have access. It specifically requires the individual causing the test to be performed, which in most instances is clearly the physician who orders the test, but it can't be done without the laboratory, to inform this individual of to whom such tests will be available.

Now there is a current debate ongoing between the New York State Task Force on Life and the Law and the New York State Health Department as to what that means because does that restrict to whom it is reported, or does it only require that the patient be informed of to whom it is reported. Under our HIV confidentiality, it only said you had to tell them who can get the result, it did not change who can get it. So the physician who orders it, all of his agents, the insurer who pays for it, potentially your employer if they are the ones who pays for the public health agency, there was a long list of A to M of who can get access to the results.

The Health Department believes that it did not change who can get the result, it only said you had to tell the person who can get the results. That will play out. There is no case law yet. Sorry, I am talking like a lawyer. I slip.

The process in terms of reviewing the laboratory is, yes, the laboratory is asked for each assay for which it seeks a permit in genetic testing to submit all of the market material, because we assume that is where they explain the test to the physician, any materials they have prepared for the patient, because we assume they are the ones who educate the patient as to what test is being done, what the limitations of the test are. But the physician has to explain to the patient the impact to them and their family. So it has to be a joint effort. So we can look at the technical materials the laboratory provides. We are certainly not looking at the conversation that the physician has.

There is a problem. Many physicians, and I'll pick on a few and I'll be specific, take, for example, Factor 5 Leiden mutation detection being ordered by hematologists in coagulation assessment laboratories. They are used to ordering lab tests. Implied consent of the patient. Stick out your arm and have your blood drawn. They don't understand the genetic implications of the detection of this mutation unless we educate them. You know, the issue of if we find it in you, then we have issues for your children and your parents who may be at greater risk because they are at older ages or may be more amendable to intervention because they are at younger ages. So they haven't thought about that aspect of this assay they're ordering.

Many laboratories that are hematology labs are being pressured by their primary client, the hematologist, to add this assay. They have never thought about genetics either. They do quantitative hemoglobins or whatever coag factors in a biochemical sense. They weren't intending to detect an inherited genetic condition. So they think of it as a simple hematological, yes, no, we find it, we don't find it assay.

When we insist that they implement a consent form, because clearly the statute requires it, and that it be explicit and it talk about all of these issues, their solution to the problem is to put on the requisition form a signature for the physician's signature, he has to sign to get the test done anyway, that says I've taken care of it. Whereas we would prefer that the requisition form incorporate the specific consent document that explains the test.

While if you're offering 50 different genetic tests, does that mean 50 different consent forms under our statute? Yes. And to have a different requisition form for every assay for every genetic test and you are going to do a panel of tests based on ethnic background, it becomes extremely onerous, not only to the patient, but to the physician, and then to the laboratory.

So what is happening is labs are asking us is it acceptable for a physician to simply sign saying I've taken care of it. We can't tell the physician he can't do that. We don't regulate the practice of medicine. Our only alternative would be to tell the laboratory you can't do the test under that circumstance. And no one is suggesting that we interfere with access to appropriate testing, technical appropriate testing.

So, yes, we look at the consent documents, yes, we look at the materials the laboratory produces. We require them to produce them. I can't require the physician to use them.

DR. McCABE: Francis? And we're going to have to, I know this is generating a lot of interest, but we're already beginning to run behind.

Francis, briefly.

DR. COLLINS: So I'm in the same state of confusion that I think Reed's question indicated he was as well in terms of how this actually all works in practice. It does seem as if there is a real opportunity for collaboration but also for duplication. So, quickly, if I am a lab that I have just set up and

I want to do Factor 5 Leiden testing, to take your example, Dr. Willey, and some of the samples are going to come from New York State, and I have decided because it seems like a trendy thing that not only am I going to offer this, I'm going to market it to physicians in my local area and advertise this as a test they should be doing before they prescribe oral contraceptives.

So I would like to know what would I do as far your organizations in order to be compliant with your guidelines, because certainly Factor 5 Leiden appeared on some of those lists, and would any of your organizations actually prevent me from carrying out this marketing strategy, which I think at the moment is probably not scientifically validated; namely, to do this as a genetic test prior to the prescription of oral contraceptives.

DR. WILLEY: If you're going to do business and receive specimens from New York, you seek and obtain a permit application from New York. If you wish to practice within the standards set by the professional organizations, you're going to obtain copies of their documents, review them and evaluate whether they work for you in your situation.

So New York State --

DR. COLLINS: Where does NCCLS fit into this?

DR. WILLEY: You would purchase from NCCLS a copy of the document -- I'm on the board of directors of NCCLS, in case that is a disclosure of interest -- you would purchase from NCCLS the current proposed document, which is in the process of final revision as an approved document. But it is a guidance document. It is for your perusal and use if appropriate in your circumstances. It is not regulatory.

DR. COLLINS: And who would organize my proficiency testing?

DR. WILLEY: You could purchase that from CAP. And if your state in which you are located has a contract with CLIA and is inspecting you locally to issue you a CLIA certificate, because that would be required for you to carry out this process, you might choose enrollment in CAP as your PT. You are not required to participate in any PT. You are required to assess your proficiency twice a year. If you are going to do business in New York, you are going to be inspected by New York. New York is going to inspect your PT or proficiency assessment results. You are going to submit your marketing materials in this scenario only to New York, no one else is currently looking at these materials, and our reviewers might very well comment on what is the scientific basis of your proposed marketing scheme and could say no in New York.

DR. COLLINS: But if I were not receiving specimens from New York, that step would not occur by any of the other mechanisms?

DR. WILLEY: As I understand it, no.

DR. McCABE: What I'm going to do now, because I've seen about half the panel who have their hands up and we don't have time for the discussion, I'm going to ask that our four panel members have coffee in the Parklawn Room with the group and we can huddle there and try and get some of this clarified.

Then I would ask that the four panel members maybe go into the overflow room and try and think about, if you were designing a partnership, how you might organize this to be effective and streamlined in a public-private partnership, and perhaps come back to us. I don't know if any of you are going to be here

at the end of the day, but perhaps someone could discuss that toward the end of the day. Thank you very much.

We are going to take about a 10-minute break for the panel and the presenters in the Parklawn Room.

(Recess.)

DR. McCABE: Ann Willey has asked me to clarify one point, and that is on technical validity versus clinical validity. In New York State, the validation is all at the technical validity step because no laboratory has submitted data regarding clinical validity, and she asked me to clarify that.

Let me tell you a couple of things that have happened. One is that, thanks to Dr. Boughman and the hospitality of the University of Maryland Baltimore Campus, it looks very likely that our meeting for the public consultation on January 27 will be held at the University of Maryland Baltimore Campus. I think this has a number of advantages. One is that the cost of the venue is decreased. Second, we are definitely outside the beltway, which I think is an important statement to make. It is about ten minutes from the Baltimore-Washington International Airport, four blocks from the Inner Harbor. It is an auditorium that holds about 500 individuals with approximately 10 to 15, maybe even 20, breakout rooms convenient for smaller groups. I think that we're still finalizing this, but the auditorium is available and we're moving forward with that plan.

The other thing is that I talked to Dr. Bob Martin briefly, and I don't know if this will work out, CDC was planning a summit to discuss some of these issues that we're addressing in terms of genetic testing and the regulation of genetic testing. We are looking at possibly getting together the day and a-half before that public consultation meeting in the Baltimore-Washington area someplace, if it works into people's schedules, put together a reasonable size group that can actually try and develop some plan and try and put something together before our February meeting in a little more detail than we'll probably be able to do today. But I would still appreciate it if the panel members, working with Pat and perhaps other people involved in the CLIA process, over the noon hour could begin to think of how we might tie some of this together.

So, let's move on now to discussion of the CLIAC recommendations for genetic testing. There is a letter from the CDC, some summary material on CLIAC recommendations, and a copy of Pat's overheads from the presentation in June at Tab 11. We have got roughly a half hour. We're running a bit late already and we need to break early for lunch. So, sorry to put the time pressure on everyone, but if we're going to finish up today, we're going to have to stay with the schedule.

So Pat?

DR. CHARACHE: We have just gotten audiovisual arrived. It will be here in one second. What I'm going to emphasize during this half hour is first I'm going to give some definitions to pull together the definitions that you've heard Dr. Noll and others use that pertain to laboratories with the terminology we've been using, clinical validity, analytical validity, and clinical utility. Then I'm going to give examples of the testing recommendations which have been made by CLIAC and which is being implemented by the CDC. And I'm going to also emphasize some of the issues which have not been defined by CLIAC and for which the people at the table that you've just heard this morning have major contributions to make as well as this committee itself.

And I would like to make one other point; and that is, the difference that we see between the speakers you heard this morning and CLIAC are that Dr. Willey and CLIAC have regulatory roles, the other speakers have voluntary guidelines and standards which are thoughtfully produced but do not have

the force of regulation. People can choose whether or not to follow them. So Dr. Willey in New York State is a regulatory approach as is CLIA. The CAP is also regulatory in that it is a deemed organization through HCFA. So HCFA and 22 organizations that it has deemed have regulatory authority to ensure that the CLIA regulations are being carried out.

So that is the answer to the question asked by Francis and Reed, the difference is regulatory versus voluntary. And that is also reflected in part in those who draw up those regulations. Although CDC has relied very heavily on voluntary groups in formulating its regulations, CLIAC, which has come up with the genetic regulations, is a voluntary group, and is, although we're called special government employees and get an honorarium which is really very generous, it doesn't quite cover our expenses.

So we will go on now to consider definitions. And I want to contrast the ones that are used in the laboratory, which are the pre-analytical phase, analytical phase, and post-analytical of laboratory testing, and show how that fits in with the terms we've been using in this committee. I'm not going to go through all of this, but I would emphasize that some of the components of the pre-analytical phase include issues such as: Confidentiality, informed consent, test ordering practices, provision of information that's required to perform the test or interpret it, specimen procurement, transport which is appropriate to the test, laboratory assessment of the appropriateness of the test. All this happens before you start the test.

Now the definition of appropriateness and what have you addresses the issue, which I won't repeat, that Dr. Willey summarized so clearly, which is test validation. Many of the components of what is regulated address the issue of whether this is or is not a valid test. In the CLIA format, we have looked at a couple of issues which are less defined in New York law, and I know New York law because we have paid Dr. Willey $1,000 for Hopkins, such as the number of kindreds that have to be tested to say the test is valid. And the CLIAC recommended a different number for tests with a low prevalence in the population than the number of kindreds which have to be assessed for high prevalence tests. Now I won't go through all of this, but there is a long list of what is incorporated in the analytic phase that you have to address and those which are in the post-analytic phase of laboratory testing.

The post-analytic phase does include the results return, including confidentiality of the return and how you do this, the results format, the content, which as to be included in the result, the method of results return, who gets the report, role of the genetic counsellor, role of the director, the specialist, and so on. So all of this is included in the post-analytical phase.

If we put these together with the terms we've been using, you can see that the pre-analytical phase includes a lot of components which are being discussed that are required to assess clinical validity and clinical utility. The analytical primarily addresses what we have been calling analytical validity and clinical validity -- sensitivity, specificity, predictive values. And the post-analytical again, like pre-analytical, heavily addresses issues of clinical validity and clinical utility. But there is overlap in all of these. It is not an absolute.

Now what I'm going to cover in the rest of this discussion, and I would invite the committee to interrupt if they have a question that they would like to ask in real time rather than coming back to it, is the need for a separate category for genetic testing. I am going to give as examples of pre-analytic phase recommendations informed consent and appropriateness of the test. In the analytical phase, I will comment on personnel, proficiency testing, and a very important issue that hasn't come forward but on which we want to ensure that we get some input from the public, which is the reuse of samples. In the post-analytical phase, I'm going to show result interpretation. And then I want to give an example of how one could monitor this in our surveillance edge of the regulatory process. And I am going to comment, as Dr. Howell and others have stressed so very elegantly, the need for physician education to make any of this work. No regulation is going to work without that component included.

The separate genetic testing category has been recommended by everybody, NIH, this group has commented positively on it, as has CLIAC and CDC, which is implementing CLIAC recommendation. This is particularly important in being able to emphasize the components of test validation and the special requirements that are necessary for genetic testing. The precedent for this exists already in regulations. There is a separate category for cytology, as an example, and there are special requirements for other components. But we want to make as unique as cytology is genetic testing.

This is an editorial comment which I flagged, which is that I think the implementation can be speeded up and get the attention of CDC in moving it to the top of the pile, and also HCFA, if there is support from SACGT. Now the first step to get this implemented is what is called a Notice of Intent. CDC has drafted this but it would help if this group says they want this Notice of Intent to be moved forward faster. That Notice of Intent simply tells the public what the proposals are going to be to solicit public input on these specific CLIAC proposals.

DR. McCABE: What's the timing on that?

DR. CHARACHE: The draft is ready. It is in the iterative stage. But I think if this group says that you really do want a separate category, it will speed it up by perhaps a year. But I think it would go through right away because it is ready to go through.

DR. McCABE: Is there anybody on the committee that feels that we should not support this recommendation?

(No response.)

DR. McCABE: Hearing none, I'm going to suggest that we do make that recommendation then to the CDC from the Advisory Committee. We've never done anything by motion before I don't think, but perhaps, given that this is a formal request, we should do it formally. Does anybody wish to make a motion to that effect?

DR. TUCKSON: I so move.

DR. McCABE: Do I hear a second?

DR. LEWIS: Second.

DR. McCABE: All in favor of the motion to encourage CDC to move forward with this, please say aye.

(Chorus of ayes.)

DR. McCABE: Any opposed?

(No response.)

DR. McCABE: Abstained?

(No response.)

DR. McCABE: It's unanimous.

DR. CHARACHE: Thank you.

DR. BOUGHMAN: Mr. Chairman, would we now have a letter go directly to the CDC or to the Secretary encouraging the Secretary to contact the CDC, or both?

DR. McCABE: I don't know that we know the answer to that.

DR. CHARACHE: I think this can come forward from this group, if they want clarification. But it's the request for the Notice of Intent, which means that there will be public discussion.

MS. CARR: Could Judy Yost or Bob Martin comment on the mechanism through which we should get this to the right parties. The letter in our notebook was from Ed Baker, who is the Executive Secretary of CLIAC, to me, as the Executive Secretary of this committee. We can go back that way if you want, if that would be appropriate.

DR. McCABE: Could you go to the microphone, please, Judy?

MS. YOST: I think that the letter needs to go to the Secretary of Health and Human Services only because there are clearly operational implications with that recommendation. So that both agencies are able to fulfill that.

DR. McCABE: Okay. And Sarah, should it, in terms of our reporting structure, should it go to the Surgeon General or to the Secretary? Do you want to clarify that and we'll get it to the appropriate party.

MS. CARR: Yes.

DR. McCABE: Thank you for helping us with that.

DR. CHARACHE: Thank you.

Now I'm going to give some specific examples under the pre-analytic phase, analytic phase, post-analytical phase. And the one I've chosen to outline here is the issue of informed consent. The CLIAC recommendation is that there must be informed consent for certain sensitive tests. So the recommendation is that for sensitive diagnoses, the laboratory may not perform the test until the appropriate consent has been provided.

Now you will see in Tab 8, the second article in there if you want to look at it later on, Margaret McGovern, first author, has done a survey in which she showed that 70 percent of genetic testing laboratories have that statement but only 6 percent follow that. So our recommendation is that the sample should be processed only to the extent required to stabilize it. So if you have a sample that needs to be stabilized, you stabilize it, but you don't perform the test. And this would then be a federal regulation. If you require consent, you don't do the test unless you have it.

DR. BURKE: And Pat, could you comment on what would be a sufficient evidence that consent had been acquired, particularly vis a vis our previous conservation. For example, if the physician sending the sample in had signed the form saying I have provided appropriate consent, would the laboratory have then met their obligation?

DR. CHARACHE: Okay. These are some of the issues which were not completely addressed by CLIAC. One is, what counselling must be provided to the patient or family to make sure that this is a

valid consent; who is authorized to provide the informed consent; what is an appropriate consent; and what tests or groups of tests are considered "sensitive." So I think the question you ask was not fully defined. Now what we have done in our laboratory for a parallel model for HIV testing where consent is necessary, the laboratory won't run the tests unless they get a copy of the signature of the person who has requested it and a witness.

DR. BURKE: A copy on the informed consent?

DR. CHARACHE: A copy of the informed consent.

DR. BURKE: I think this is a point worth just registering at this point, because even if we had detailed and very satisfactory answers to all those questions, from a regulatory point of view, what the lab requires to meet that recommendation is really the crucial issue. And if it is just the agreement by whoever is sending in the test that these criteria have been met, what it really is doing is shifting the burden of responsibility to the test ordering physician.

DR. CHARACHE: No, we are not recommending that because CLIA has the control of what the laboratory does, and therefore we are requiring that they have the documentation in their files of the informed consent. This has worked well in our experience in the HIV example. The requisition can be very simply designed so that you don't have to see everything; you don't have to see what the patient has read, but you have the part of it which includes their signature.

DR. BURKE: I just want to clarify, and I think Elliott has a comment too, I think that we're getting into a tremendously important area. I am not actually suggesting at this point that laboratories should formally review and determine that each different step has been met once it has been defined. It may well be that it is appropriate that that responsibility reside in the arena of the ordering physician rather than the arena of the lab. What I'm really concerned about is that we be very clear about what kind of regulatory mechanisms have what kind of teeth. And to the extent that we're simply asking a referring physician to certify yes, yes, I've done these things, we need to be clear that the lab is not providing any oversight over those activities.

DR. CHARACHE: No. Here our recommendation, which will be modified with public comment, is that the laboratory have that documentation. And that is largely driven by the fact that physicians lack education. They think this is not really important, or they don't do it with the precision that we feel should be under observation.

MR. HILLBACK: Could I make a comment because I think we need to be careful that we don't try to make the laboratories the policemen of the whole system. If we don't trust the physicians, and I'm going to watch Reed come out of his chair in a second, if we don't trust the physicians, and we're not willing to take steps to push the physicians to be able, then I think we're lost. Because this whole thing is dependent on the whole system working. So I'm very nervous about trying to decide that the laboratory has to be the policeperson of this entire system to make it work.

DR. BURKE: I agree.

MR. HILLBACK: I think it assumes a major mistrust of the medical community, which I think is impossible given the pervasiveness of these kinds of tests 20, or 30, or 40 years from now. So I understand the point, and we do not do a test in our lab until we get informed consent. We stabilize the sample and we stop. So we agree with that. But to go to this step, and then how many other things we will start asking the physician tell us that you know how to do this or how to do that, pretty soon we are the policemen of the system. And I don't think anyone really wants that.

DR. CHARACHE: Elliott, I think the point here is that these are the issues which are open for discussion and which CLIAC felt that input from this group and from those at the table here would be very important in terms of drafting the final regulations.

DR. McCABE: Judy, and then Michele.

DR. BURKE: And I think you need to add to that, I think as we consider these tests, I think what this interchange tells us is that as we consider the answers to these questions, we really need to be thinking in practical terms about what are the oversight action implications of each of them.

DR. CHARACHE: Exactly. And that's why I'm emphasizing what I really hope this group can focus on. I think it is really important.

DR. McCABE: Judy, and then Michele.

DR. LEWIS: The other thing is, as we're rolling this out and as we realize this is going to become a significant activity as we get more and more genetic tests, I would like to see us get a little more generic in our language and start talking about health care professionals rather than just physicians because there are other people who are ordering tests and who are doing primary care and who are going to be educated, such as advanced practice nurses, genetic counsellors. So I just want to make sure that the language we use is sufficiently inclusive, that it is not restrictive, because many patients are getting primary care from other than physicians these days.

DR. CHARACHE: I use the word "clinician."

DR. LEWIS: That's fine. But I keep hearing physician.
DR. CHARACHE: That was intentional, the word clinician.

DR. LEWIS: I keep hearing physician and I just want to be careful that we don't just say physician.

DR. CHARACHE: Point well taken.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: There is a model out of the immunization program that can be used for this, at least the pediatric immunization program. The National Childhood Vaccine Injury Act requires a process of informed consent before any vaccine is given. There is no oversight, that is self-policed. There is no regulatory body that oversees what goes on in the health care provider's office. But that is a regulation.

DR. McCABE: Judy Yost?

MS. YOST: Just a point as a regulator of reality. We can't give the laboratory responsibility for something it has no control over. So we have to be judicious in how that is applied. So your points are very well taken because, coming from a laboratory originally, I see where you could put the laboratory at a disadvantage. So it is important how that --

DR. BURKE: And you might actually believe you were providing oversight that you weren't.

MS. YOST: Yes.

DR. BURKE: Because it simply wasn't doable.

MS. YOST: Right.

DR. McCABE: Muin?

DR. KHOURY: I guess my comment relates to the issue of appropriateness of testing. I saw in your earlier slide in the pre-analytic phase the two areas of clinical validity and clinical utility are covered. I would like you to explore with this group to what extent those parameters have to be known in order for the test to be appropriately performed?

DR. CHARACHE: I wonder if we can come back to that subsequently, because that is one of the things that we actually would hope that this group could help define.

DR. McCABE: And just before we move on, to reiterate Elliott's point, and I'll speak for Reed, but I think there are serious issues having to do with the practice of medicine and that there would be serious concerns about interfering with the physician's role in the practice of medicine. I am sure that organized medicine would have strong opinions on this.

Yes, David?

DR. FEIGAL: Just as a quick comment. I think you'll find that most of the HIV requirements are regulated by the state medical records confidentiality practice of medicine. The teeth there is that they license the practitioners in a laboratory. So I think if you had a state where informed consent wasn't required, you put a laboratory in a difficult position to say that they can't run the tests unless they have it. But it will make it a little more challenging to approach this across all 50 states.

DR. CHARACHE: Well, I think this is, as I pointed out in the slide, I think these are areas in which this body, as well as those at the front table, can help define the strategy which would be extremely helpful.

In the interest of time, but addressing the question which was just asked, these are some of the issues which have not been fully defined by CLIAC to date, which are: What tests require what kind of clinical information; how can ordering needs be best communicated to the clinician so that they provide the information that is required in a smooth manner; who determines whether a test is appropriate or not, and in the laboratory side there are three levels of people who could be participating in this, and I'll come back to who they are; and then how should the laboratory address samples that can't be stabilized when the information is not readily available, and can they accept the fact that the information will be provided at a later time. So there's a lot of issues here that need to be fleshed out and that are absolutely essential.

Analytical phase, and in the interest of time, again I'm not going to go into detail on a lot of these. But there are specific testing requirements that have been defined by CLIAC which go beyond those that are regularly monitored but are included in some of the things that Ann Willey's group review as well. But this would be at a national level. They define personnel categories, and requirements for education, training and certification, also defines the responsibility for each job category.

For genetic testing, there were recommendations made to upgrade three of the personnel groups. We felt the people actually performing the job probably were already adequately covered, and I'm not going over what is already adequately covered by CLIA, there is a lot that is already covered. But in the

case of the laboratory director, the important thing is what Elliott pointed out yesterday, the director is responsible for everything that goes on in the laboratory, including assurance that no test is performed that is not useful to the patient. And that is the current terminology which would be clarified. The technical supervisor is responsible for the test itself, the pre-analytical, analytical, and post-analytical components, including how and when it should be ordered, how to interpret it, et. cetera.

In many of our smaller laboratories, all three of these job descriptions which are defined in CLIA and for which recommendations have been made may be the same person. They don't have to be three separate people, but they have to meet the requirements for each of these tasks.

In the analytical phase of testing --

DR. TUCKSON: Excuse me. One thing on the director.

DR. CHARACHE: Yes?

DR. TUCKSON: We heard yesterday in about half the states you can walk up and knock on the door and get a test without a clinician having certified it, if I remember from yesterday's discussion. Legally, how do you hold the lab director accountable if an individual demands the test?

DR. CHARACHE: The lab director has to decline to perform it if it's not appropriate. We can discuss how this would happen. I had not considered that, and CLIAC didn't consider that.

DR. FEIGAL: You probably have to change the state laws that say patients can order their own tests.

MR. HILLBACK: I have no experience in our 30,000 or 40,000 tests a year of anyone ever trying to do that with any of our labs. So while it may be in the law, we have absolutely zero experience. I'll check with our medical director, but I don't think we've ever had an instance.

DR. McCABE: Well, we heard yesterday of an individual family member who had this done for hemochromatosis. So we know that it is available.

If you can wrap up in the next five minutes or so, Pat.

DR. CHARACHE: Okay, I will. I am going to skip the next one. This issue of retention of samples is very important. This group hasn't considered it, but it is one that we're looking forward to getting comments through this Notice of Intent, and that is that there are specific purposes for which one needs to save the sample and have it available for reuse. In some cases, such as a quality control reagent for future tests, all patient identifiers can be removed, in others, not. And this is a major issue, particularly with congressional action in this area, of needing to discard samples. So we do want to get input in that. And there are components of that which have not been fully defined to the present time.

The post-analytical phase, I've covered that it is associated with results interpretation. In that area, which has a great deal of detail already written, we have to address the question of whether the test can be run if the clinician promises to provide the data at a later time; what form the information is conveyed; and so on. So there are areas here also in which we hope the Secretary's Committee can provide some thought particularly in these areas.

There are strategies for determining whether all these things have been done. They can be done through the survey monitoring process, and there are some issues here that we would focus attention on.

I'm going to end with two brief editorial comments, and these are mine, not CLIAC's, but I see a need to expedite the program, which you've already taken the key step to do. I think it is necessary to understand our definitions and be sure that we understand how they fit together; to understand the interwoven strengths of the private sector, which has been very heavily used as consultants for CDC, not only in CLIAC but in a special proficiency test venue in an initiative with Dartmouth on the education issue, plus all of the major players here, and we have to coordinate these strengths. I think a beautiful step in this direction is being taken today here.

But I have underlined and made particularly clear that we must identify the resources needed to develop and maintain the agreed upon program. HCFA will be very comfortable if it has the resources to run a proper survey. They will be resistant to playing a role if they don't have these resources. I think this is very thoughtful and appropriate on their part. But this committee has got to ensure that the resource need is understood.

And, finally, I have emphasized the need between the genetics community input in program, the role of the laboratory specialists, and the regulatory specialists and their need to integrate their programs.

DR. McCABE: Thank you very much.

Just before we leave this though, what I would suggest is that the panelists, Pat, Judy Yost, Bob Martin, and anybody else who can fit at a table at lunch, gather around the table at lunch time and begin to have some discussion of this issue and coordination.

Now we're going to move on to discussion of oversight Issue 3, Options for Oversight of Genetic Testing: Possible Approaches. It begins on page 30. Elliott Hillback will begin the presentation and will explain the consortium concept, then Kate Beardsley will explain the options for analytical validity and clinical application.

MS. BARR: Could I just throw out a straw dog for a moment?

DR. McCABE: Yes.

MS. BARR: We've talked about not interfering with the practice of medicine. And I would suggest that there are countless interferences with the practice of medicine today that we need to be very sensitive -- managed care, economics, licensure, et. cetera. So there are times when we may want to, for instance, suggest that licensure include something. So it's not a sacred cow I guess.

DR. McCABE: No, no, no. But I would worry about the political forces that might be moved in those discussions. But certainly it isn't a sacred cow.

Elliott?

MR. HILLBACK: Thank you.

What we tried to do in the numerous conference calls we had and in-between times in trying to lay out a spectrum of options, because we felt that our mission at this point time was not to try to settle on an option, but was to try to lay out a range of options that captured the kinds of things that might reflect different types of oversight that this committee eventually might want to recommend. But until we had heard from the public, until we had heard from a number of the experts that are here and a number more experts that I'm sure we'll hear from, it was presumptive to try to go to an option and say this is the option we want to present.

So what we tried to do was create a range of options. What I would like to do for a couple of minutes is just think a little bit philosophically about some of the issues that are embedded in those options. I'm not sure they're as clear yet as they need to be as I started to think about this the last few days. It may be that the document itself needs to be modified before we go out to the public to reflect the thought process that's here.

So let me sort of start with a couple of overview transparencies that lead into the thought process rather than start directly with the options. Pardon the spell-checker. Wherever you see a smudge on these slides, that's where my spell-checker kicked in about 5:30 this morning.

To me, the fundamental mission that we're focusing on as a group starts here. And I want to start with this and move down to where we tried to define the range of options. Our job is to make sure that our health system uses genetic information to help individuals, not necessarily always patients, I think we sometimes assume that people are always patients, and the rest of the society doesn't use the same information to harm the individual. So I think that's the fundamental point that we need to think about, that it is holistic.

So where I go from there is to my definition of oversight, which is that it should be viewed in the broadest sense with the objective of improving that provision of health care, not solely as a laboratory regulation or regulatory mechanism. I think if we fall back on that, we're doing ourselves and the whole committee a great disservice.

It is a system-wide issue, and I think we should be thinking system-wide as we think about oversight. It's what gets me up off my chair a few minutes ago, is that we start thinking about here's the lab over here, and here's the rest of the system over there, and somehow it's not an integrated whole and I think that's a very silly position for us to take.

So from point of view, I make some basic assumptions. There are lots more of these, I'm sure I've left out lots of favorites of other people, but these are what helped me get to the next point. One, that knowledge growth is iterative, my favorite word, and rapid.

That knowledge growth is system-wide, not point-sourced. That means that the laboratories don't have all the information. In fact, they have a small part of the whole information. If what we're trying to do is improve health care, we're not trying to improve just the laboratory performance, therefore we have information that is coming from hundreds, thousands of sources -- practicing physicians, practicing genetic counsellors, practicing nurses, and a lot of researchers who are all or none of the above, and the labs -- and, therefore, we have lots of different sources of information that we have to somehow integrate.

That the migration that we heard about yesterday from single-gene to multigenic and combinatorial type tests will be fairly rapid and common. We will be moving from a relatively simplistic set of operating parameters to a much more complex set of operating parameters, whether that is in the lab, or in how to use that information, or how to integrate that information.

And test volumes in general I think for most of these specific tests will be somewhat limited. We are not going to have the million test march. Generally, each test is going to be done on a limited, focused market of limited, focus group. There are the exceptions that will become general screening tests or that will be focused on larger groups of individuals. But generally they will be small.

So the therefore for me is that the systems that we have to think about, that we're chartered with giving some advice on, have to be, one, largely service-oriented rather than kit-oriented, because all of

these things -- speed, and information coming from lots of places, generally small volumes -- argue very strongly that this is not a kit-oriented provision of tests, this is a service-oriented provision of tests. And that provides a number, as we've talked about already a bit over the last couple of days, a number of unique challenges for oversight.

Where this takes me is that I consider sort of a two-part piece to this. One is we need to create a process, very important choice of words, process that recognizes the nature of this knowledge creation and that somehow has built in process controls in the process that monitor but also accelerate and support the process of knowledge generation. One of the fundamental issues, we'll hear more about it from Muin, is this knowledge gap, not the therapeutic gap, we have that all the time, but the knowledge gap.

The uncertainty level on the first day that we find a gene is immense. And that level of uncertainty falls generally in fits and starts, in my opinion, and it falls relatively slowly and in a very disorganized way. If you are a lab director and you are board certified and you're obliged to sign out every test and to give the best information you can, it's a scramble to keep up to date and to be completest and to feel comfortable that you are giving the best information at any point in time. It is not a system, it is an ad-hoc approach at this moment in time.

And the idea that we could improve that rate of knowledge generation to narrow that gap is very important. So one step in any system that I think we need to put in place of oversight is to maximize the knowledge creation and to somehow formalize it, to centralize it, whatever the right word -- centralize, I hate to use it when I'm in Washington because it sets off all sorts of good alarm bells.

But there's an "and" at the bottom of this. So if we'd go to the next slide, please. The other point is that once you have this information, you have to communicate it. I think one of the concerns that is always expressed is the accuracy of the communication. So one of the key parts of any oversight process we build in is how to make sure that the information is accurately communicated to the users, the users are primarily practitioners, and I wrote M.D.s but I will go back with my spell-checker and correct that, Judy, and their patients.

So to me, the fundamental system of oversight, if it only focuses on the knowledge generation piece, it's lacking, if it only focuses on this piece, it's lacking. It needs to encompass this entire process. I don't have the magic answers of how do you maximize accurate communication. Francis and I have some fundamental disagreements about the word "marketing" and what various people do when they market. We'll deal with that. But I think we need to deal with this issue of accuracy. And I think Wylie used the phrase, but lots of us have used it over the last several years, which is, tell people what you know and tell people what you don't know at any point in time, and tell it to them accurately.

I think one of the fundamental issues that this drives me to, and I think what we tried to reflect in some of the options, but tried to give the full range, is we have a fundamental question we have to ask, and put your engineering cap on for a minute. Are we managing a "flow," which goes to Pat's four dimensions, which I still can't visualize, but that's okay, lots of things I can't visualize, are we managing a "flow" process or a "batch" process.

If you're managing a flow process, and there are lots of engineers in the world that do this, there are lots of products that are made this way, you build in controls that operate while the flow is happening without interruption of the flow. In fact, many of the manufacturing facilities in the biotech industry operate that way under flow control systems that are reviewed by FDA, and I'm sure FDA has lots of people who are experts in the theories of flow control and managing flow.

The other approach is to take a batch approach, which says you make a widget and then you inspect it after you've made it and determine whether it is appropriate or not, whether it meets your

quality standards, and then you make another widget, or you make a batch of widgets and you sample from that. But you stop the process and start the process.

I would argue that the flow approach is an important concept for us to get our hands around. Maybe we need some expert help to do that. As an example, in the current environment, which is more laissez faire than flow control I suppose in some people's minds, but Genzyme Genetics has gone through nine different versions of our CF test in the last nine years. We started with one mutation, we are about to launch an 86 mutation test, our most recent was 70 mutations. We are actually dropping 7 mutations and adding 23 new ones to try to create a test that focuses on some subpopulations that we need to provide testing for. On a batch system, I don't think we would be at 86 mutations today. On a flow system, we are.

And so I think when we started to think about the range of options, you have to include both of these approaches because they are both potentially appropriate. But I think as we look at the range of options that Kate will talk about, we clearly wanted to include some options that were primarily and fundamentally based on the concept of flow rather than batch.

So this is the thought process that we kicked around over various conference calls and tried to define some options that would provide this range and therefore stimulate the debate on what is the appropriate type of oversight to provide.

So let me turn it over to Kate for a couple of minutes and let her explain the options.

MS. BEARDSLEY: Elliott, do you want to talk about why we divided this?

MR. HILLBACK: I was going to talk for a minute about analytic validity and clinical validity. I think the principles have been talked about a lot in the last two days. And in the interest of time, we did separate those two because they are usually done sequentially, they could have different types of oversight because they have different ramifications. Analytic validity doesn't tend to have the same level of flow, and therefore a batch approach might be more appropriate there than it would be, in my opinion, in the other. So we did separate this into two sections; one that dealt with analytic validity, and one that dealt with clinical application which combined clinical validity and clinical utility.

DR. McCABE: Thank you.

Kate?

MS. BEARDSLEY: I think Elliott's already stressed, and I want to stress again, that the options we've defined here are certainly not all of the options. Just kind of ones that people thought about. And I don't think that we should have any expectation that what we're finally going to end up with here is necessarily any of the options that we're talking about today.

As Elliott said, we divided the options into two sets of options. The first of which have to do with overseeing analytic validity. I think of analytic validity I guess as sort of the bedrock of a test, because if it's not analytically valid or it doesn't have an appropriate analytical validity, it's got nothing. And while we have I think spent more time talking about clinical validity and clinical utility, in some ways analytical validity really is the core, or part of the core at least, of what we're talking about.

The first option that we've got here is what we believe to be the current situation, in which the lab that is offering the test is required by CLIA to measure analytical validity and, as I understand it, the lab director is not allowed to let it out unless it's a reasonably reliable test. HCFA, through CLIA and through

the deemed organizations, do inspect labs, as we've heard about earlier today, and look at the work that's done underpinning analytical validity now. The first option is to maintain that current system.

The second might be characterized as beefing up the current system. Basically, the lab that offers the test would still be determining its analytical validity, but we would strengthen the CLIA standards and rely more on the professional associations, some of which we've already heard from this morning, and I think also have more frequent inspection. We would still have HCFA, CLIA and the deemed organizations be in charge of enforcement.

The third option is different in kind I think in that it involves a premarket review of tests before the test is used in clinical application. That we've set up as an FDA review, since FDA generally has done premarket reviews in this context, although it wouldn't necessarily have to be an FDA review. Elliott mentioned the consortium, and Muin is going to talk about it more. One thought is FDA would essentially look to the consortium for establishing the standards that it would use in conducting its premarket reviews of analytical validity. And, again, enforcement and monitoring would probably have to be the responsibility of FDA under this option.

And finally, the fourth option is a more standard FDA model, the model that's used for tests that are sold in kits. Again, the lab always determines the analytical validity. FDA then reviews that data, and a premarket review is done and FDA decides whether it is appropriate to use the test in clinical use. And FDA also does the enforcement.

So those are the four options that we've come up with on analytical validity.

We have also come up with four options on clinical application, which is a combination of clinical validity and clinical utility. We had a lot more options and we've worked hard to try to get them down to something manageable. So you will see that some of these options have suboptions within options here to try to get them down to a manageable number.

The first one is intended to be, again, the no-change option. But the laboratory that is offering the test is required to determine its clinical validity and determine its clinical usefulness. That is, as I understand it, right now not a CLIA requirement per se, but a lab director under CLIA has a responsibility to be responsible. And some people I think would say that determining clinical validity and clinical utility falls within that responsibility to be responsible.

At the moment, there probably is no real enforcement of what labs are doing here. FDA has established what they have characterized as some minimal enforcement, and I believe that HCFA has pretty much stayed out of this area. So that's the no change option in the first choice.

The second choice is like the second choice in the analytical validity situation, a kind of beefed up model of the same thing, where CLIA and the professional associations would be probably more active in setting standards in this area, and HCFA would be more active in making sure that those standards are enforced.

Option C builds in the consortium idea, the notion that we should have a public-private partnership in overseeing these tests. The consortium would not only be involved in actually collecting the data, but in some models maybe even creating the data. And again, Muin is going to talk about that later as we go on. If we had a consortium that were establishing standards, we would probably be looking to HCFA and the professional organizations again to be doing the enforcement.

And, finally, Option D, which is the FDA model. Again, the lab that is offering the test would be

determining its clinical validity and usefulness. This is the only one that involves a premarket review before the test is offered for clinical use. We have tried to show here that there are a number of different kinds of standards on which FDA could operate if it would have this responsibility. FDA's standard standard for approving tests is that the test is safe and effective. If that's not going to be appropriate here, and it sounds like the data gap is so substantial that it's probably not going to be appropriate for some, there are other kinds of standards that FDA could also use, and we have tried to name a couple of them.

That's what we've come up with, and I guess we're discussing it now.

DR. McCABE: Yes, please.

Yes, Pat?

DR. CHARACHE: I think my favorites have disappeared between our last conference call and this summary in a way. I wonder if we could put the overhead up and let me show --

DR. McCABE: Which one?

DR. CHARACHE: Well, let's put up first the analytical validity and I'll make a point, and then I'll make a brief point on the clinical one.

DR. McCABE: B or C?

DR. CHARACHE: The four options. Option B. I think everyone agrees that the current status needs to be beefed up considerably. One of the Bs that we had before was that the strengthening of national and professional organization standards was described also as major input by professional groups, more of the consortium approach to establishing the regulations which would then be monitored by HCFA and CLIA.

The next one, which is C shows, if we could put that up, shows the consortium approach. But the change is that this is suggested that it would be enforced by the FDA. I think the FDA really would have a problem setting up a duplicate structure as opposed to having it monitored through CLIA. So I like the concept but I think to have a second regulatory monitoring body set up would be a problem.

MR. HILLBACK: Pat, can I just comment on these.

DR. CHARACHE: Yes?

MR. HILLBACK: I think in the interest of trying to reduce the numbers, we did do some skinnying down.

DR. CHARACHE: Yes.

MR. HILLBACK: But I think implicit in B up there is that there are lots of ways to skin that cat. There are lots of ways to strengthen the CLIA system, and there are lots of ways to strengthen the enforcement by CLIA and we couldn't capture that whole range of possibilities. But I think assumed in that was professional organization involvement. And because virtually all of our lab directors are part of the professional association, it was implicit that these laboratories were involved as well.

DR. McCABE: Okay. So B would cover that then?

MR. HILLBACK: So I think we're okay on that one.

DR. CHARACHE: Okay. Fine. If we could then go to the clinical one. Because there are challenges, if the FDA has to approve everything in advance, development would stop. It's just a volume issue there.

On this one, we don't need A because it's got to go. B is then, as in previously, Elliott, is the consortium approach that the standards would be developed with input from all relevant people. Okay. And then the HCFA and the deemed organizations would be monitoring. Okay. So that then is what used to be a lower number.

MS. BEARDSLEY: Pat, I'm confused. This is the CLIA-plus consortium?

DR. CHARACHE: That's right. But with the consortium approach. But they would be developing the standards. Obviously, it has to be a government regulatory body that regulates as opposed to recommends.

DR. COLLINS: Isn't the consortium approach C, not B?
MR. HILLBACK: The one that's in the middle though -- yes, go to C.

DR. CHARACHE: Let's look at C.

MR. HILLBACK: It's the full consortium.

DR. CHARACHE: Yes, because these have changed since our discussion.

MR. HILLBACK: This was really aimed at the front-end problem of knowledge generation and collection and improving the input, improving our knowledge base, closing that knowledge gap. So that whole part in green was added as we went from B to C to reflect that labs on their own only have some small part of the data in their control and to gather it is beyond their means.

DR. CHARACHE: Okay. Well, what we would say is that, as in the validation discussion that we heard from Ann Willey, that the laboratory director has to have that in their laboratory and be familiar with it. It doesn't address how it's generated.

MR. HILLBACK: Right.

DR. CHARACHE: Okay. The next. Okay, this brings the FDA in, which is a different concept than previously, and adds the challenge of the FDA having the capacity to review tests before they're implemented, and also raises the issue of setting up the separate FDA monitoring program which would be very costly.

MR. HILLBACK: But I think in the interest of what we were trying to do in terms of setting a range, it would have been inappropriate for us to take this D case and not have it.

DR. CHARACHE: Oh, yes. I think that's right.

MR. HILLBACK: If you ask my personal predilection, I wouldn't put the D case in.

DR. CHARACHE: Yes. No, I think that's right.
MR. HILLBACK: But then I might face some charges of being biased. So we wanted to include

the range of options that exist. And the D case needs to be there. It is an option.

DR. CHARACHE: So we will read then perhaps either B or C as meaning that best input is derived into generating the regulatory requirements which are then monitored by CLIA.

MR. HILLBACK: The difference between B and C in this slide is in B we really are not addressing how to generate knowledge better. We're only addressing building some sort of a collaboration, call it a consortium, whatever, to build better standards to upgrade what we do today in terms of the standards to be set that labs have to live up to.

DR. CHARACHE: Okay. I appreciate that.

MR. HILLBACK: But then C adds in the concept which comes from Muin and the group, not just Muin, he keeps reminding me, but lots of people that are working on this, to improve our ability to generate knowledge so that we can close that knowledge gap. So that's the new feature of C versus B. Otherwise, they are pretty much identical.

DR. CHARACHE: Okay. I think I now understand what we'll be addressing. It was a change. I appreciate the clarification.

I would also then, finally, recommend removing the tables which I think are misleading. It says, for example, that at the present time FDA monitors tests. And I asked Steve Gutman who said that they have input in less than 1 percent of tests. So I think that table would have to be changed.

MS. BEARDSLEY: Let me just say, we put in the table in an effort to make it easier to mix and match these options. But I think you're not the only one who feels like we've really oversimplified the thing. We've been both overinclusive and underinclusive in those tables. And so if there is widespread feeling that that's the case, we ought to just take them out.

DR. CHARACHE: Thank you.

DR. McCABE: Judy?

DR. LEWIS: I think this is an important concept. Elliott talked a little bit earlier about the fact that we were starting with the health care system to make things safe and effective for individuals. I think that part of what we're doing is we're looking at a whole bunch of trees and not necessarily looking at the whole forest. I'm a little bit concerned that, as we focus on oversight, the major thing we're focusing on is laboratories because I think there's an awful lot more to the process. And I think if we start with the level of the individual rather than the level of the health care system, we are going to start to focus on what's important to people.

And I would hope that we wouldn't be premature enough to put some of this stuff out until we actually hear from the individual humans, that is our goal to hear from when we have our January meeting, because I think that part of what we're doing is framing the realm of possibilities without having all of the people present to tell us what the possibilities are. And I don't want us to be premature in listing options and in focusing on laboratory standards, which I think are important, but I think are only a very, very small piece of the oversight issue.

DR. McCABE: Yes, our goal at this meeting is not to make that final decision because we want public input on it. Our goal at this meeting is to have a document that we can understand, because if we can't understand it, then probably the public isn't going to be able to understand it.

DR. LEWIS: My point is if we frame the possibilities where basically the people who aren't here don't have an opportunity to help participate in what the possibilities are. And I think we might be going a little bit further than we need to in terms of framing the possibilities.

DR. McCABE: Well, we need to have some discussion of that.

Dr. Feigal?

DR. FEIGAL: I think one of the things to remember as we look at the possibilities is that we are talking the set of genetic tests that are largely in the home brew category that differ from the traditional commercial tests in that they are low volume, as was pointed out, and that they may be changing rapidly. And I think those are the features that we're grappling with. The genetic tests that make it into the mainstream, that become commercialized in a kit, they will be regulated the way that FDA regulates other in vitro diagnostics.

So the issue really becomes what are the tools that are necessary to do that. One of the things that I think needs to be put on the table is that we may not have the tool that we need from either the HCFA kind of process or the FDA kind of process. That doesn't mean that we can't propose changes. And to the extent that they don't change laws and only require changes in regulations, those can be implemented within reasonable amounts of time.

So I would say when we talk about, well, current status or FDA this or HCFA that, don't assume that we have to cram the current tests into one model or the other. There are other ways of doing things.

DR. McCABE: And there is a precedent for interagency activity on this in the CLIA. So we know that that can work.

Francis, then Wylie.

MR. HILLBACK: Can I just expand on that for one second. I agree. One thing I still feel pretty strongly about -- I don't know how many tests will move into, as you call it, the mainstream. We do more CF tests than anyone else in the world. We have continuously evaluated making a kit out of our test and selling it and it still isn't economically viable for us to do. So I think we should think that way. But I do think we need to be thinking out of the box and not get hung up with history in terms of whose done what.

The only other thing I wanted to add, Ed, we did make a decision that we would defer some of the other part of the system discussion on the user community until a different time, even though I think that's part of the total oversight issue. But we said there's no way we're going to take on the education of the M.D. community and how do we interface with the M.D. community better now and get that done. I just want to make sure that everyone who wasn't on our subcommittee phone calls recognize that we just made a decision that we had to defer that at this point.

DR. McCABE: Francis, then Wylie.

DR. COLLINS: Taking what Dr. Lewis is saying about the need not to overly specify the options, I think I'm also a little worried that we've broken this down to four possibilities as though there is something special about them. And I actually thought the tables were somewhat helpful because they allowed you to see there are four kinds of choices that you make. And so you have three possibilities from Column A, and three from Column B, and so on. And that makes it pretty clear that you have a combinatorial range of possibilities that is pretty large even though the table picks out four out of many

larger numbers.

I wonder if in formulating this, in terms of this document, if it would be more useful to try to be more explicit about that. These are the four places where input could occur, and those are the four columns in these tables, and in each one of those here are some options of what that input might be -- whether there is premarket review or not; whether there is enforcement, and if so, by whom. And then simply them put forward as examples, making it very clear that these are not options that have a particularly strong merit to them, but say pick four examples. Maybe they would be these four, maybe they would be related to this. That might in fact help somebody look at all of this complicated set of opportunities and think through how it might be worked out in a certain circumstance.

But again, instead of calling them options, as though somehow SACGT had narrowed down to these as the synthesized minor universe of possibilities, instead use them as examples. And maybe four is the wrong number, and there may be arguments about which specific examples ought to be chosen. But make it very clear that there is no intention here to say these are the only ways we could go.

MR. HILLBACK: I agree totally.

DR. McCABE: Why don't we, instead of calling them options, why don't we change them to examples. And why don't we lay out the principles first, and then specify a little more clearly among those principles what the examples exemplify. I think that really could be a lot more instructive to somebody who hasn't been in on all these conference alls.

MR. HILLBACK: I think Francis is also right in that when we did make the charts, which we didn't do early on but were suggested later, I think it does give that flavor of you can mix and match, which I think is really where we will end up. If we ended up with one of those four stated options exactly in that form, I would be very surprised. So I think we can take that back and try to reflect those comments.

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

DR. BURKE: I would like to comment that I think, putting together everything that we've heard this morning, we I think are hearing that there already is a very effective oversight mechanism in place that particularly has to do with lab procedures, basically with what I think we're calling analytic validity. It includes proficiency testing, it looks like it's a very cooperative set of organizations working together. And probably the biggest challenge in that particular part of oversight is the need to prepare for a vastly increased volume and the possibility that volunteer organizations can't keep up with it.

But if we take into account that piece we probably already have a good vision of how to do and it's more the logistics of how to do it in the future with more tests, I think we then have to acknowledge that we haven't heard anything really effective in place or perhaps even feasible regarding appropriate use of tests, assurance of pre-test counselling, informed consent, post-test counselling, what sort of information gets back. What I'm hearing is it, first of all, may be unrealistic for the existing mechanisms to have those tasks attached to them, and it may even be unduly restrictive to create regulatory mechanisms that might restrict patient choice about access to tests or might interfere with clinician judgement about use of tests.

I come back then to the fact that everybody needs good information. I think we have kept coming back to that as a theme. That is, if we say, yes, there are already in place good oversight mechanism to make sure labs do what they're supposed to do and we simply need to see how to build on them, but that we need a better way to assure that appropriate test use occurs, it seems to me that is fundamentally what

Elliott just described as a communication issue, the communicating to people what we know and what we need to know. And I just want to throw out that it might be that is the fundamental oversight or fundamental regulatory task, which is to ensure that there is a method for gathering and disseminating that information.

MR. HILLBACK: Accurately.

MS. BARR: Thank you.

DR. BURKE: Accurately.

DR. McCABE: Yes. And let me just make a comment about NCCLS. In addition to what we heard from Dale about their committee structure, the other thing, and you'll see it in their catalogue, they have instructional tapes and disks that they put out also that they can then inform individuals about how to go about this. I am bringing this up just because I was involved in doing one for newborn screening recently. So that this is intended for the nurses in the nursery and the clerks in the nursery so that they can acquire the information that is necessary to have that test performed.

One might think of either NCCLS, one of the professional organizations developing this for at least the high volume tests and then something perhaps more generic for the lower volume tests. But I think that we're going to need some sort of instructional approach like that, because just putting things in print media probably isn't going to really be effective. It needs to be very targeted and specific.

DR. BURKE: Another mechanism that I think we've already seen labs use very effectively is information that comes back to the physician with a test result. That sometimes can be a really key aid to a physician in dealing with a test that they don't use very often. And I think there probably is room for that piece, too.

DR. McCABE: So review of the post-analytic as well as instructing on the pre-analytic.

DR. BURKE: Yes.

MR. HILLBACK: I think the whole communication issue, we've talked about it a lot, but it is fundamentally about having the knowledge to communicate as well. I think that all those pieces fit together. I think Wylie's point is right. But it is not just the process of communicating accurately, it is knowing what to communicate, having that knowledge there in some form to communicate it.

DR. BURKE: And communicating lack of knowledge.

MR. HILLBACK: Yes. Exactly.

DR. McCABE: Reed, and then Pat.

DR. TUCKSON: Yes. I'm excited by the direction of the conversation. In addition to the points made, I would wonder if it's possible in the chart to indicate or footnote it as to the implications of the different recommendations regarding FDA versus CLIA versus HCFA, those kind of things. I'm not sure I understand still what all the implications are when we see model 4 that says, okay, the main folks are the FDA. What does that trigger in that substantially different than the triggering in if HCFA does it? I think just having a little explanation of the implications would be helpful as we look at that chart.

DR. TUCKSON: Pat Barr, and then Pat Charache.

MR. HILLBACK: Can I just comment on Reed's comment? I think that could be useful. I think it is very hard to do because I think there are lots of opinions about what the implications may or may not be. We can try to gather that but I would want to make sure that we gathered it from the agencies as much as from the non-agency people that are involved so that we have a balanced perspective. I've created a fundamental difference between flow and batch thinking, but what does that mean? I haven't tried to flesh that out. I am sure the agencies have various thoughts about the pros and cons.

So we tried at one point in time. I have lots of yellow pieces of paper with ideas about pros and cons, but I had a tough time doing it. Maybe we can take that on, but I would like to get some thoughts from various different players and make sure it is a very neutral point of view that tries to lay out the pros and the cons.

MS. BEARDSLEY: I think the other thing that one might say about that is that it is not necessarily the case that any particular agency has to go with any particular regulatory model.

DR. McCABE: The comment was that we don't have to tie a specific regulatory agency to any of these models. We can be a little more creative in looking at that.

DR. TUCKSON: Ed, I'm sorry. But I'm actually glad to know that this is not as straightforward as it may appear. If this is as difficult as it is, I'm glad that Ed and his team are willing to step up to the plate and take the challenge. If it requires another sort of really good look at this, then let's do that, because, at the end of the day, we are recommending back to the Secretary the use of her armamentarium of bureaucracy. If there are implications that are different for each of these sorts of tools, we need to be really on the same page.

DR. McCABE: And there are fiscal implications we have to recognize also.

MR. HILLBACK: I think the one thing we might want to think about is whether our recommendation is more along the lines of some of the things that Dr. Buchanan said yesterday and some of the things that we've talked about in terms of what any oversight process should include or not include or what it has to make sure it does and doesn't do, rather than to say you should deploy this person to go do that thing. We don't know as well how the agencies work or could work or could work together. I think one of the approaches we may want to think about is rather than the agency focus, in the long run is to say here are the issues. We like flow versus batch, if that's what we like, or we like batch versus flow, if that's what we like.

DR. TUCKSON: And let them figure it out.

MR. HILLBACK: And say, okay, now given that, how does that happen. And we also propose very strongly that it is not agencies by themselves, it is not the government by itself if this is going to work. So we could think about some options that way.

DR. McCABE: Okay. I have got Pat Barr, Pat Charache, Michele, Joanne, and Judy.

MS. BARR: While I liked Elliott's preliminary explanation of what we were doing, I have to say I disagree with him in terms of where he wants to take it in terms of his last statement. I think that we have an obligation to think through what we can think through and make recommendations where we can make recommendations.

But what I think yesterday and today so far has done for me, while I was satisfied more or less with the document before, I am very unsatisfied with it now. And one of the things I think we have

completely left out, if we're putting this out broadly to the public, is a statement of what we would like to know from them. Which of the professional groups should be involved? Should anthropologists be involved? Should psychologists be involved? Should lay activists be involved? At what point should they be involved?

What do consumers want from a genetic test? Why would they ask for a genetic test? Are there six questions that consumers should be armed with when they go to a doctor who might recommend a genetic test. That's a great educational tool, folks. Your doctor can't answer your questions, you're going to let the doctor do the thing the doctor wants to do, or is the doctor going to go out and get the answers to the questions.

So I think we should even broaden our table if we can to try and include other kinds of players at other points. It is different ways to answer the questions actually that Pat framed that we don't know the answers to within the lab process. And then perhaps we can give it to the lab if we have ways of gathering that other information.

DR. McCABE: Pat Charache?

DR. CHARACHE: Two comments. First, you have a handout of the slides I projected. I think, Wylie, you will see that a lot of the issues that concern you about what should be in the report are regulatable through CLIA. I have listed examples of what the report has to include to guide the clinician.

For Pat Barr, also regulatable is what information has to be available to the physician. No laboratory can do a test if it doesn't have a clinical consultant, which can be the director, who can provide the answers to the physician who has ordered the test and provide guidance to the physician who has ordered the test.

So I think a lot of these issues are regulatable, are in CLIA, and are being addressed by CLIAC. What is missing is what Pat emphasized, Pat Barr, and that is, those lists of areas in which the information is not currently available in CLIA to provide some of the details that could be test by test specific or groups of test specific. So I really would like to strongly endorse what Pat Barr has said, that these are areas in which regulations need to be amplified and addressed, and this is a consortium area, for sure, including leadership through this committee, this task force committee.

The second issue I would like to come back to is the question of what examples, not options now but examples, we want to put forward. And I would also strongly support the recommendation that this get a second iteration. So that our seven conference calls, which have now been reduced to something we just saw today, can have review of what the recommendations would be.

Perhaps it would also be very helpful to include what the FDA does, what CLIA does, and what HCFA does if it is not clearly enough stated already. Specifically, that the FDA is the location for review of tests that are marketed. They have the ability to look at the home brews and for regulatory purposes have elected not to. But they look at tests. CLIA looks at laboratories and laboratory processes, including what information you have to have to validate a test, to offer a test, and to record a test. And then HCFA agrees with the regulations and agrees to monitor it, and then deems professional organizations to do a great deal of the monitoring.

DR. McCABE: Yes. I think that's in there on page 18. You might want to look through it and see if it's not clear enough.

Michele?

DR. LLOYD-PURYEAR: Actually, Pat Barr said what I was going to say.

DR. McCABE: Okay. Joann?

DR. BOUGHMAN: In the beginning, there is a new test.

DR. CHARACHE: Is that in seven days?

DR. BOUGHMAN: Maybe seven days. In that new test is inherent processes through which that should go to determine several of these parameters. And having been on FDA panels and so on, in fact this is where it is at that point that we are going.

At the same time in the beginning, there are all of these generic, ethical, and professional questions both focused on the laboratory and the broader set of professional interactions that have to be developed and put in place for this test to in fact be done correctly from beginning to end. That's just in the beginning. And we've heard several different ways where we have begun to address those, not with just the laboratory professional organization, but with the broader professional organizations as well.

Then we move to actually performing tests by lots of laboratories under lots of different conditions. And in fact, right now, this is a plea from one of the people that was on those conference calls to in fact increase the framework that we have put in our tables here which actually mixes in the beginning and after the beginning and really limits to the laboratory phases, and does not ask the question from the patient's perspective what the steps are before it goes into the laboratory and what the steps are that would be outside the laboratory and who and how those might be monitored, overseen, or whatever. Which is where, in fact, more clearly some of the professional organizations may come back in in a different kind of way than we were speaking about them over the summer months.

DR. McCABE: Judy Yost?

MS. YOST: Just a comment again from the regulatory perspective. I think it is highly important in this area, because it is so dynamic, and because it is so complex, that regulatory agencies do collaborate with the professional standards organizations in developing not only what the standards need to be, but even guidelines about how to enforce them. I think you want to leave the least amount of judgement to the individual who is going to enforce those requirements to ensure consistency when evaluating an individual laboratory.

I think it's really important that that guidance be provided. It doesn't have to be a regulation, it could be a standard or a guidance, but specific information to help those individuals who will enforce the requirements whether they be standards organizations or whether they be regulatory. I think that's really important because I think then you lose the potential of consistency in enforcing the standards and implementing them.

DR. McCABE: And Victor?

DR. PENCHASZADEH: I have a couple of concerns that have already been voiced. But perhaps one of the major concerns in what we've seen is all the analytical part of the test is probably the least controversial or for which we have more mechanisms to assess and control and monitor. One of my concerns is actually the introduction of new tests, something that Joann just mentioned. Not only the introduction of a test, but also the specific indications of a particular test. This will be on the question of what type of information we need to determine whether a particular test should be introduced, and for

what indications, and for what population, and so on and so forth. I am kind of confused at this stage, on the basis of all the options or the examples and so on, if we have really addressed a mechanism for defining that or an option or actual example.

Now I have to say also that I am kind of confused whenever I read the FDA regulations and mandate and the question of the division between home brews and kits. If we are saying that most of genetic tests are going in the direction of home brews and being marketed as services, I get the feeling, but no one seems to be very forthright on this, that it would seem that the FDA regulation system is not flexible enough to come up with one of the requirements that was said that we want a flow system rather than a batch system.

And I guess we need some clarification, or at least I need some clarification, on one, whether the decision, and this is addressed to you, Dr. Feigal, whether the decision of the FDA not to regulate the home brews is something based on lack of resources or on the feeling that it would be too batch-type of approach that would delay introduction of tests, or what it is due to? And if there are hurdles that they identify for the rationale behind that, whether it is something that this committee could look into and recommend appropriate steps in the right direction?

DR. McCABE: Just a comment. We knew that the group was going to break early. They decided to break earlier than they had originally planned. So we have delayed and we can continue our discussion. So we will let them go through the line first.

I have Elliott, Kate, and then Dr. Feigal.

MR. HILLBACK: Well, I was going to ask two questions now. One was to get some clarification from Joann. But I think to come back to your question, Victor, I don't know whether we want to assume whether FDA could put together a system that could cope with a flow environment versus a batch environment. Again, should we presume that they can or can't. They manage a lot of manufacturing plants that use a flow system, including the one that we have, so I am sure that the thought process isn't alien and they have a lot of smart people. But that's where I come back to what do we want to recommend. What are the key measures, what are the key components of oversight or who should do it. I'm not sure we can debate that.

I wasn't sure, Dr. Boughman, you're taking out the issue of time in this and going back to a snapshot sort of a point of view? I just didn't understand quite.

DR. BOUGHMAN: No. I think one of the problems, at least in my own mind, is that for the introduction of a new test with new measurements or result formats, whatever, that would be more of a one time initial proving of all of the validities and utilities and usefulnesses and efficacies. Then once that is into the process, then it becomes an extremely dynamic situation that, in fact, is broader than our charts cover.

As new places start to do the tests, as new groups of individuals or new professions, whether it goes from the geneticists originally into the oncologists, but as a test gains more predictive value it may move into internal medicine or family medicine. I think those things are the issues that we really in the long run are dealing with.

MR. HILLBACK: I'm not sure that first time out of the box is always the critical point. Because if you say we have a new test, it is clinically useful for one person in a million, but for that person it is clinically useful, fine, it gets "launched." But over the next ten years, it goes from being clinically useful for one in a million to one in ten thousand. That is really the difficulty is how do we keep changing it.

The one in a million is I think a fairly simple hurdle for most of these tests to get over.

DR. BURKE: It's a simple hurdle, but often that restriction, that limitation is not well articulated. And, actually, I think there is a tremendous need to articulate precisely those limitations in the early stages of tests.

MR. HILLBACK: No, I agree.

DR. McCABE: Kate, you made side comment to me.

MS. BEARDSLEY: What I said was that it seems to me that we might benefit from trying to define a little bit more carefully than we have what it is we're doing here. We started out I think with the notion that we were building off Chapter II of the Task Force Report and that what we're talking about here is the safety and efficacy of genetic tests. And when we think about it in terms of the analytical and clinical validity and clinical utility, we are thinking of it largely from a scientific framework. And I think there has also been a fair amount of discussion today about thinking about the effectiveness of a test from a patient protection point of view, which is mentioned in the write up but doesn't have the central place that it's had really in these discussions.

So those are two pieces certainly of what we're talking about when we talk about safety and effectiveness. It might be useful to figure out whether there are other pieces that also need to go into that definition before we try to make the document reflect what we're really talking about.

I think the other thing that could use some definition is the idea of what oversight is. We are a committee that is reporting to Dr. Satcher, who I'm sure is interested in the overall system by which genetic testing is happening, but probably is particularly interested in what role the federal government should be playing as opposed to all the other players in this. And so we had focused to some extent, although not exclusively, on the parts that the federal government might play.

If we are now saying, no, oversight is really a much bigger thing than that and there are a lot more players and we want to define all of the players and what their roles should be, then I think we're talking about something quite different. So I really would like, if it's possible, to think a little bit about what exactly it is we're doing here.

DR. McCABE: I'm going to let everybody think about that and we'll come back to that. We will just finish up this round with Dr. Feigal, and then I want to for the last ten minutes of the morning or so really focus on Kate's issues.

DR. FEIGAL: Let me answer your specific questions before I make some other comments. The issue of home brew to us is that the clinical laboratory that is making the home brew is a manufacturer. The law doesn't differentiate between different kinds of manufacturers. So we implicitly have the authority to do all the usual kinds of requirements with home brew.

Home brew is a little bit special though because it is occurring in the setting of a laboratory which has its quality assured through the CLIAC and the CAP and other types of processes. And so as we set our priorities of where we get involved, we look at the risk-benefit and where to prioritize our efforts. And this is an example of where we have looked at the fact that there is overlapping oversight of the clinical laboratory that provides some standards level for home brew. So that the resource issues, which are real but shouldn't be what we make our decisions on entirely, that is one factor.

And then, the other side, is that we have thought about the benefit side. Which is that a certain

amount of R&D happens in these kinds of settings that would be discouraged if someone had to fill out all the types of manufacturing issues. And the whole paradigm of how commercial or manufacturers are thought of I think doesn't quite fit with where some of the science is taking us, where we might have a test that has a single customer per century, something that is so customized that just for this one patient we're after that one gene and we're not going to repeat it again.

What my general comments were, I actually wanted to just make some more comments on sort of the differences between the CLIA and the FDA emphasis. As has already been said, the CLIA emphasis is really in the quality of the practice of clinical laboratory medicine. Some of that has to do with how well they evaluate tests, their proficiency with them, many of the things that have to do with the quality of how the tests are performed.

FDA is given the responsibility that products be well-manufactured, that while they're experimental they be done with certain kinds of protections for human subjects, and that at the time of market entry there is an evidence threshold that is set out in the law by Congress for different types of products, and when you meet that evidence standard you actually lose some of the burdens that you have while you're investigational.

If you think of it from the patient standpoint, what do you lose when FDA steps back and doesn't take regulatory discretion? And this area is not unique. For example, there are products that the FDA does not have any requirements for premarket introduction -- over the counter products for which there is a monograph. Any one of us could manufacture aspirin and put it on the market without getting prior approval from the FDA because there is a monograph that sets the standards for doing that. We'll come around and inspect you some day. But that's an example where we've taken a different approach and used a standard process to say here's a whole class of products that we think can be competently made in this way.

But from the patient's standpoint, even if you think about the issue of informed consent, when does a genetic test stop being experimental? When it is first introduced there is even the question of sort of the competence of this lab to do this test which has no track record with this test, it's got other relevant things it may well point out. Who assures that the tests are well manufactured, that the reagents are well manufactured, that the kinds of procedures are in place to do the test properly?

The whole basis of FDA even evaluating that something is ready for commercial prime time and entry into market is usually based on the notion that it isn't just going to be the inventor that's using the product, that in fact they've got something and it works reliably in multiple places. And I think, again from the patient's standpoint of view, those are things that are of concern.

But I think if we sort of broke down a little bit what our goals are, we wouldn't have to focus so much on who is doing them. Because I think we have, particularly in the quality of the laboratory work, there is a lot of overlap and a lot of different ways. And I think we could get a long way by defining what it is that we're concerned about.

I think that we want the products to be well manufactured. We want the laboratories who are actually doing the manufacturing in the case of home brew to also follow other good laboratory practices, such as recordkeeping, the other kinds of things that have been mentioned that don't have much to do with manufacturing. We're interested in good clinical practice. And where that relates to the FDA is when products are still experimental. There are different rules for physicians or clinicians who are providing experimental products.

And then the final thing that I guess has sort of been on the table, and one of the presentations this

morning talked about the oncology model, is the whole notion of who's the guardian; is there regulatory oversight of evidence, of claims. When it is a commercial manufacturer, there are rules of evidence for what they get to state. And stated simply, if you have demonstrated something with good science, you get to brag about it in your marketing and your advertising. And if you haven't, you either don't get to say it or you have to put a lot of caveats on it.

If we say that in fact there is sort of no market entry for these products, then we lose sort of the experimental phase. And we lose sort of the rules of evidence that exist for commercial products where, if someone says this measures your cholesterol and that's of benefit to you, you can say what's the evidence for that.

I'm not saying that these aren't the right things to do. But these are the things that we need to grapple with. What is it that we really want to accomplish. From a patient standpoint, with a brand new home brew from a single lab, what are the concerns at that level. And then when you've got a group that's really become the world reference standard on something like CF genes or something like that, that's a completely different situation. But what is it still reasonable to claim.

The flow versus batch, you're quite right, that really isn't an issue for us. We have a mechanism for companies to submit modifications in their manufacturing and their claims structure and they vary from things which they can do themselves and report to us in annual reports or not report to us at all, to other things that have been judged a little more sensitive where you have to come in with more evidence, and it's cumbersome and it's slow relative to the other mechanisms.

But I think we can ground ourselves a little bit if we can come back and say, well, okay, the patient walking in the door, what are their concerns going to be. Because some of these things will fall to the states, some of them will be tools that CLIA can help with, some will be tools that the professional groups can. Evidence may best come from some of these consortiums, public private consortiums; it may not come from hardly anyplace else. And then there are other things that relate to manufacturing and things that would be more traditional FDA or good clinical laboratory practices that would fall back more to HCFA, CLIA, those types of things.

DR. McCABE: Let me go through some of the things I've heard, getting back to Kate's point, in trying to synthesize and lay out some items just to make sure that they are covered to try and give ourselves some additional charge.

I've heard a couple of people talk about test introduction. I certainly think that this is a concern for the patients. When is a test ready for prime time? When does it move from the research laboratory to the clinical laboratory? I can't remember right now how it's addressed in here, but I think we need to clarify that.

The other things that we have included in here but we need to clarify a bit are the analytical validity, the clinical validity, and the regulation of those. And we've talked about how we would go about doing that.

We've talked about some issues this morning again getting back to what does a patient want to know. A patient wants to know that their practitioner knows why they're drawing a test and what they're going to do with it. We have questioned whether some of the practitioners really would understand the genetic implications of that. So we have practitioner education, and then we also have patient knowledge, patient education.

So those are a few of the things that I've heard putting down as a list. I had a much longer list,

but what we really have is sort of overlapping sets and there are different ways of sorting through this.

So, other thoughts? Pat, then Elliott.

MS. BARR: Just another way of looking at it, which I think we just heard, is organizing around what is often called premarket, then market, and postmarket. I think one of the difficulties in genetics in these kinds of tests is that we desperately need postmarket data and that we need a way to both gather and get it back into the system. I think that is what Muin's going to talk about later. But I think if our document in some way could explain what the differences are as well as what the agencies are, we would be getting closer to what we need.

DR. McCABE: Okay. Yes, Michele?

DR. LLOYD-PURYEAR: Within that context, if you can explain what exists now and what needs to exist, that's what's missing from the chart, actually.

MR. HILLBACK: I think one of the things from Dr. Feigal's comments that we really have to remember is that we in genetics seem to set a higher standard in terms of the issues of clinical validity and clinical utility. Because analytic validity, before we would put any test into the market, anyone, we would prove that the mutation we're looking for or the genetic defect we're looking for is what we find. His comment was that a cholesterol test has to prove that it tests for cholesterol.

The next question is, is the requirement there on the laboratory to show that various cholesterol levels or, in fact, levels of different lipids have various outcome impacts and various clinical utilities? No, not in this day and age. It is accepted that cholesterol matters, although lots of different lipids are being tested now to define that. I think we have to be careful that to say that we don't have a step before a test goes in to make sure that it is accurate is not accurate.

The problem we have is that the timeframes quite often to understand utility are very long, and that's what we don't always have. We have some limited understanding of utility. And that's where we always come back. We came back to this in the Task Force on Genetic Testing. I guarantee we will come back to it here with this group. That's the complicated part.

DR. McCABE: Pat, and then Michele.

MS. BARR: But you can have premarket approval.

DR. CHARACHE: Yes. I'd like to reinforce this issue of needing standards for test introduction. As I pointed out, the components of ensuring that the test has been validated is covered by CLIA, but the CLIA inspectors only come around every two years. So the test could have been introduced and be underway before this occurs, and that isn't there, although I think working that out is going to be an issue of how much time it's going to delay test introduction and that kind of thing. But, certainly, the components should be specified and codified so people know what they are.

And then I'd like to add one other thing, which is, as I say, started very nicely today, which is not redoing what has already been done or what is already underway by the groups that spoke this morning as well as the CLIA and CLIAC initiative which is well underway. I think that Judy's point that the guidelines that are already developed and so thoughtfully done need to be modified and reviewed and implemented. It would be extremely important to HCFA and the oversight committee to be able to use those documents as opposed to starting from scratch and perhaps missing something that should be in there.

DR. McCABE: Michele?

DR. LLOYD-PURYEAR: I would just like to go back to what Elliott said. A test for cholesterol is not the same as a DNA probe, it's not the same as a test for lead levels, it's not the same as a test for hematocrit. Because a level of your cholesterol means something, there's an average, it means something; a certain lead level means something. But a DNA probe looking for a mutations means something to one individual that it doesn't mean to another individual. So you can't compare. I keep hearing that comparison of throwing out a cholesterol, that we're doing something different to the companies.

MR. HILLBACK: All you're saying is that we're farther down the curve of closing the knowledge gap.

DR. LLOYD-PURYEAR: Yes, but that's a significant difference, though. CF mutations means something different to an African-American versus somebody from Northern Europe.

MR. HILLBACK: Right. A specific mutation means -- right.

DR. LLOYD-PURYEAR: It's just that you have to make different kinds of demands on the companies that are producing those tests that you would for a cholesterol level because of the knowledge gap.

MR. HILLBACK: But you're still back to the fundamental issue I think. You have a lab director that signs out the lab results that says I did this test and here's the result.

DR. LLOYD-PURYEAR: But they don't know what it means.

MR. HILLBACK: Well, if there is utility, the assumption there is utility, that there is some value in doing the test even if it's to get a negative result that says we know what the negative result means, we're not sure we know what the positive result means. We talked about that yesterday.

But the problem is that we do have this knowledge gap at the beginning. The issue is to say what we know and what we don't know. The alternative is to do nothing, is to say we won't make this test available until we know.

DR. PENCHASZADEH: Well, there is a minimum --

MR. HILLBACK: And then the question is, till when? One week? One month? One year? Ten years? BRCA1, how long do you wait?

DR. McCABE: I'm going to let Wylie have the last comment of the morning, and then we're going to break for lunch.

DR. BURKE: I think your point is well-taken, Elliott. I think what we're saying is in the current regulatory environment for tests that aren't genetic tests, in general, we expect a certain amount of clinical validity, some knowledge of clinical validity before the test becomes available. But that clinical validity might be referent to a particular population and a particular use, yet the test is available for plenty of other uses as well and we don't regulate on clinical utility.

I think one of the difficulties we have is that we can see very clearly that information about clinical validity referent to different uses in different populations is crucially important in the use of

genetic testing, as is clinical utility. And I think one of the basic questions before us is, is to what extent should those become the subject of formal regulation?

DR. McCABE: Okay. That's a good way to end the morning. We will resume at 1:00 this afternoon.

(Whereupon, at 12:04 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:09 p.m.)

DR. McCABE: Let's go ahead and get started.

A couple of things that I just wanted to mention. One is, people have been asking about the logo. I've learned the origin of the logo is that, if you look at it, it becomes completely clear once it has been decoded for you, and that is to the left there is the sort of gel bands, then there's the DNA, and then a person. So it is from the test to the individual is the logo. People had asked me about that.

The other thing is I wanted to talk to, it came up over lunch, is the urgency. Just one of those things I may have said to a few of you but probably haven't said to the group. Part of the urgency that I feel that we not continue to consider this is, first of all, we have a deadline and we've already postponed the deadline once. But that wouldn't be enough. The other deadline that we have, and I think is very real, is the duration of this administration.

March 15th, if we want to have an impact, we have to have something in by March 15th. Because by fall, we know what the government will be consumed with, and even by summer. So that if we as a group want to try and have an impact, I think we have to do it by the deadline that we have extended to, otherwise we're at the political whim of whether or not this group continues beyond the election. So perhaps that's putting too much pressure on us, but I think we've got to at least try on that.

Rod is to give us a one sentence summary. My understanding is that Rod has been sent as the delegate from the lunch panel and regulators group and he is to give us a very brief summary of what the deliberations were.

DR. HOWELL: We had a very nice lunch involving the professional groups that presented this morning as well as representative from the FDA, HCFA, CDC, to discuss the very simple problem, and Pat Charache, obviously, who was there. It was actually a very productive meeting because the regulatory folks and I think the professional society folks were on the same page. It was perceived that a way to proceed was that the professional groups certainly were prepared and interested to work on standards and guidelines for the practice of clinical genetics, particularly the laboratory aspects, and the regulatory agencies -- CDC, FDA, and HCFA -- were all prepared to take those data and use them for regulatory oversight.

And although there are many things that will follow from that, there were also further plans made that the group that was at the lunch table would be expanded to include other members of the group and societies and meet January 25th and 26th and come up with some more specific details of how that consortium may work. But it was perceived by our regulatory colleagues that there are certainly things in place in the organizations that would permit the guidelines and so forth to be translated into regulations and that all of that would require some work that was quite doable. So, a quick look.

DR. McCABE: Okay. And so there are existing guidelines as well as guidelines in development, is that right?

DR. HOWELL: Yes. That's correct. There are many guidelines, and, again, they will be reviewed. And Bob Martin has assumed the responsibility of organizing this effort in Baltimore with the other folks, and so that that's an ongoing work that will proceed. And it was perceived that's quite workable.

DR. McCABE: Okay. Well, thank you very much.

Pat, do you have --

MS. BARR: I just wonder if they could tell us about cost.

DR. McCABE: Probably --

MS. BARR: As they design, as they're telling us about the system, could they also tell us about cost.

DR. McCABE: Okay. As you're designing this, then look at the cost impact of what you'll be doing.

DR. HOWELL: Well, this 25-year project that took place at lunch did not get around to cost.

DR. McCABE: We appreciate your working over lunch to help begin the interaction between these groups.

A couple of other things that I wanted to talk about. It has been brought up about how are we going to vote, what is the decisionmaking. And again, let me tell you what I had been thinking though perhaps hadn't said out loud other than to a few people, and then we can discuss whether it is appropriate.

I know one of the problems that the Task Force had was coming to consensus, coming to full consensus. It led to some problems with being able to really come out with having things go as far as perhaps some would have liked. We're dealing with many of the same issues, and we're a diverse group, I think there is also the possibility that we might not reach absolute consensus.

My thought had been that if we were unable to reach consensus, if there was a significant minority that opposed the majority, that then we would frame those positions. And even if it was more than two positions, we would have people frame those positions. So that it would be the responsibility of individuals to be able to put down their positions. So that we didn't just avoid certain of the tough questions, but that we tried to at least come to the best agreement we could and then discuss where there was disagreement. Is that a reasonable way to go, do you think? Or would people prefer full consensus? Any discussion of that because it's going to have important ramification.

Francis?

DR. COLLINS: I would just counsel against having minority views on every topic.

DR. McCABE: Oh, yes.

DR. COLLINS: We should really do our darnedest to come forth with something that we can all endorse. Because to the degree that there are specific minority views, they undercut the recommendations in a significant way.

DR. McCABE: No, I would agree with that also. But I would hate to avoid a topic if we didn't reach an absolute consensus.

Yes, Pat?

MS. BARR: I think often differences may come from a philosophical difference. So maybe if we say we're going to frame our minority reports with, rather than a different proposal, but, in a sense,

with the philosophical concerns with what the majority did, we would avoid what Francis wants to avoid.

DR. McCABE: Yes, and that's what I was thinking, too, because then there may be somebody who comes along who is more creative and can figure out how that we could really resolve these. Hopefully, we could do that for most of them. But, if not, frequently I've found that positions that appear oppositional can sometimes be resolved very effectively with the right individual coming up with that solution.

Pat?

DR. CHARACHE: I think also that as the group educates each other, that we really have come to consensus on a lot of very difficult issues. So I think that information can sometimes resolve any apparent discrepancies. Certainly, the thing I commented on in the proposals, recommendations, we did come to consensus and it was just in the translation of that consensus that we ran into a few rapids.

DR. McCABE: I think sometimes when you're mired in the details of the discussion it feels like you aren't getting very far. I was pleased, some people who had been involved with the Task Force commented over lunch that we had come a long ways in a few months, which made me feel good because I wasn't so sure of that as we were leaving the morning. So just to put everything in perspective, I'll mention that feedback that I received.

The other thing is Kate and I were talking a little bit about where we go this afternoon and the fact that we want to be cautious in what we lay out for the public. Remember, the purpose of this document is a consultation document. I think there was concern that if we put out options or even examples, people are going to sort of vote on those examples and, again, we may limit the creativity of the public in terms of thinking about those.

Recognizing that by March 15th we have to come up with an example or examples that we favor and the reasoning behind that, Kate was thinking that perhaps we ought to step back a little bit from the examples and more look at what the issues were that led to the examples and try and frame those for the public discussion, recognizing that we have the options but that, with some discussion from the public, we may end up coming up with examples that we haven't laid down. And as somebody pointed out, the matrix is really pretty large from which matrix four cells were selected. So that rather than voting on one of these examples, perhaps we ought to more lay out the discussion that led to them.

We have to get to the examples by March 15. So it would mean that between January 27th and our meeting in February, there is going to have to be some work done to synthesize the information we've gotten and now see if the examples that we've laid out are the appropriate ones or if we need to consider additional ones based on the feedback we get. I would like to hear some discussion of this because it affects what we talk about this afternoon.

Yes, Elliott?

MR. HILLBACK: I agree with what you've said totally. I think the interesting comment I heard in the sort of lunchtime discussion was can we craft questions that get at some of the issues. For example, the one that Dr. Alpert and I were talking about was raising the issue to the public of the trade-off between risk and reward as you look at how much scrutiny you want to put on a test before it becomes available. That if we don't lay out that issue, it may go right past the kinds of people that we'd like to hear from and hear their opinion on that topic. Even though we think it's embedded in these gazillion pages we wrote, I'm not sure that people will extract it.

So, maybe one of our other steps that we need to do is go through and say what are the implicit questions that we think we're asking and write them explicitly so that it is clearer what we want. And there are other people that have raised other questions; Judy raised one, Pat raised one, I forget now who all did.

But maybe we've been concentrating more on this massive amount of information that we've tried to pull together instead of saying, okay, what do we really want to hear about, what are the gut issues, how much do you care about this or that. And if we can gel down to the gut issues and get input from all sides again, including the ex officio members, I think we'll have a more appropriate document for outreach.

DR. McCABE: The other thing, just to put this in perspective, we're going to have this public meeting on the 27th, but we really wanted to begin to have consultation before that and get the targeted mailings out. In order to do that, pretty much November 15th is our deadline.

So it means that those of you who were on these many conference calls this summer are probably going to be on a few more. And we may have to bring in the group as a whole at some point to make sure that everybody agrees. Some of this can be done electronically with people generating the information, but I think we're going to have to have some conference calls to sort this out. And we're going to be on a fairly tight timeframe in order to meet our deadline.

Do you want to talk about the 4A and 4B, or do you want to go back to 3 some more? Do you think that we have enough information that we could begin to frame the questions?

MS. BEARDSLEY: Yes, I think that the discussion has sort of laid out a lot of the questions. One way to do this is a more iterative process and then we would maybe say what the questions are and get some agreement on that before we then go on to try and discuss the second part of the question.

I would sort of like to go on to 4 because I think the data issues are important.

DR. McCABE: Okay. So Kate is going to talk about oversight for categories and data collection, evaluation, and dissemination, Issue 4.

Also, note before the overhead disappears, people's names who are up there and your times of departure.

MS. BEARDSLEY: I want to put up Issue 4A for a minute just so we can say what it is. It is really the $64,000 question here, and it is what do we recommend for oversight.

What we had said on the Task Force was that it was really, really, really premature to be discussing that at this point, even really to be giving any examples. And I think that our discussion this morning has reinforced that. We may need to reword it a little bit because I don't think we're talking about adding up Issue 2 and Issue 3 in quite the same way anymore. But as a principle, it seems to me that for this public document the principle should be that it's too soon to come up with any answers on 4A.

Issue 4B is about data collection. We divided it into two parts. The first part being what process should be used to collect and evaluate data, and it's principally on clinical application of test. Because our thought was that on the analytical validity questions really the lab was going to have to collect that data and it was going to have to do its own testing because those questions are very specific to the test that the lab is developing. So that this discussion was more about clinical validity and clinical utility than about

analytical validity.

We divided it into two parts. The first part being what process should be used to collect and evaluate the data on clinical application, and the second part being how should we go about disseminating that information.

In the first part, we clearly assumed that having this data is really important and we also assumed that in most cases we probably don't have as much data as we need to be comfortable. And from there, we set about thinking about what ways we could be using to collect data.

The first one is essentially the status quo. What seems to be happening right now is that every lab that offers a test collects data from as many sources as it can, maybe it generates data, maybe it collects it from other sources from the literature. But it collects as much as it can, the lab director or whoever it is decides when enough is enough to offer the test, and the lab does or doesn't continue to collect data once that test is in routine clinical use.

A second thought was that we should continue that process, that the lab should remain responsible for collecting data, but that there ought to be some national standards as to what data is enough. And that sort of harks back to some of the things that we've been talking about in Issue 3 but brings it forward to the specific data point.

A third choice is that perhaps the government could be more involved in collecting data, at least collecting it and evaluating it, and perhaps creating it. If you really wanted to take this to a heavily government oversight kind of model, you would have the government actually defining when there is enough information to decide whether particular claims could be made about the particular test.

And fourth is the model that we've talked about in other context, and that is a government/professional/industry consortium that would at least collect and analyze data, and perhaps create it, and make it available to everyone who needed. And that I think is what Muin is going to talk at more length about in a moment.

On the subject of disseminating data, we had really been thinking about disseminating data in the sense of disseminating scientific data. Yesterday, we talked a lot about the dissemination of data in the sense of marketing, and perhaps that deserves some more emphasis here because that is, in fact, another way of disseminating at least information if not data. But in terms of disseminating the scientific data, we've talked about three choices.

One is to rely on publications and professional societies, which is in effect the status quo option.

A second is requiring the lab, and again because it is the labs that are mostly using these tests, to release a summary of the information that underlies their decision to use a test in clinical use. It is not totally clear how that would be done. That could be on the internet, for example. I don't know that you would talk about it in the traditional sense of having that information actually accompany the test because the test doesn't actually go anywhere. But there are various ways in which you could ask the lab to make sure that information is available to anyone who is using that test.

And a third is, again, to ask the federal government to get much more involved I think than the federal government is now in making sure that information is collected and evaluated and that it is made available in various formats. One of the things that we talked about that is not on this slide is who needs to get this information. Is this information that needs to go only to providers, or is this information that also needs to be put into a form as best we can that will also give patients or consumers of these tests

information that they need to make choices, whether it is possible to do that. And if it is possible to do that, how it might be done.

So those are I think the principle issues that are reflected in this section.

DR. McCABE: Thank you.

Muin, you want to go to the podium? We had a document that was a summary of the two meetings that Dr. Khoury's group and others were involved in, Data Collection Strategies in Genetic Testing: DHHS Public/Private Partnership Pilot Project.

Muin?

DR. KHOURY: Thank you, Ed, very much.

What I would like to describe to you in the next fifteen minutes is essentially a framework that has evolved over basically the last year of discussion, both internally within an HHS Interagency Working Group and in consultation with two outside groups on cystic fibrosis and hemochromatosis, and talk a little bit about the purpose, the background. I think I will go through the case studies first and then end up with a framework for discussion.

Really before I start, I would like to put on the slide the purpose. Basically, to seek input on this kind of a coordinated public-private partnership to collect and disseminate data on genetic tests in the United States, and to develop some feasibility studies or pilot collection studies around two conditions: CF and hemochromatosis. And I don't mind telling you now the reason we chose these two conditions is because there is a lot of interest in these conditions. One is adult, one is pediatric. There are upcoming interventions, there are a lot of workshops and consensus statements around them, and there is some clinical utility data that is coming out. The genes have been found ten years ago for one case, and three years ago for the other.

Before I start, I would like to put on this Francis Collins' vision for the year 2010. This is the hypothetical case study that he put out in his New England Journal of Medicine recent paper in which I think a 23-year old man comes in to his health care provider, and I forgot his family history, I think he had a little bit of a high cholesterol level and a family history of coronary artery disease.

DR. COLLINS: MI.

DR. KHOURY: MI. And assuming a lot of things are in place at the time, he is offered a battery of tests and consents, and these are the results of these tests. Notice that these are inherently clinical validity-type data. Basically, it illustrates two things. One is that we're dealing with now common diseases, we're dealing with predictive possibilities, we're dealing with a combination of different genes at different loci, we're dealing with prediction of risks, both positive and negative. And notice relative risk, some of them are under 1, meaning that this person has a lower than the average risk of another person, and some of the categories are higher with even a lifetime risk estimate.

Now, of course, this is hypothetical and there are lots of hoops before we get there. And I think the clinical utility data is not embedded here, but the assumption is that this person can do something to reduce the risk of colon cancer and lung cancer and heart disease given those results of these tests.

Over the last day or so, we talked a little bit about the gap, and to me it's a Grand Canyon more than a gap. I think in order to get at the scenario, if we ever get there, and I don't think we'll get there by

the year 2010, forgive me, Francis, for saying that, I think we need a lot of things that will have to bridge the gap between gene discovery and utilization in health care. And forgive me if I have a tunnel vision on data, because I think the data of clinical utility and validity are necessary but not sufficient to bridge that gap.

So you need the data first. You need other things, too. But for the purpose of this discussion, let's focus on the data. Because in the absence of data, really there is no bridge. Integration of genetics into health care would be a little bit problematic. You can tell people that we have no data and let them make a decision. But wouldn't it be nice if we had data even though it might be limited in scope. So, to me, the Grand Canyon is what we're dealing with. This group will have a big role and responsibility in trying to come up with recommendations to cross that canyon.

So going back to the Task Force, this is old hat for you all, but for the purpose of our discussions. In 1997, when the Task Force released its report, these are what we were dealing with in terms of the data that are needed. Let me point out to you that the fourth line of post market assessment, that is what Pat referred to in the morning, is an ongoing evaluation of these three parameters, plus other things like economics, and access, and other things, will have to be collected. So it is not a static thing. You don't determine analytic and clinical validity at a point in time, you just keep accumulating more data. But we need these things in place as we go along.

So in that report, one of the many Task Force recommendations for HHS action. Essentially, "The Task Force calls on federal agencies, particularly NIH and CDC, to support consortia and other collaborative efforts to facilitate collection of data on the safety and effectiveness of new genetic tests. CDC should play a coordinating role in data gathering. In sharing or pooling of data, confidentiality of the subject source of the data must be strictly maintained." This is verbatim from the Task Force report. So since the report was released almost two years ago, we took this particular recommendation to heart.

So as a response to this effort, last year around this time we formed an Interagency Data Working Group which had representatives from all the agencies around this table, from NIH, HCFA, HRSA, FDA, and AHCPR, and CDC. We took this subject very seriously and we had several meetings over a period of a year, many phone calls, we shared documents, and we assessed the continuum of data needs -- and I will go over that a little bit more carefully -- the types of data, the core formats, how we collect data, and how we disseminate it.

And then, to crystalize our efforts, we decided to do those two case studies, first in-house. Last January, we had people from two agencies, NIH and CDC, actually review the literature, review available data, and, using some data formats, tried to fit those data into what exists. And then at the end of that exercise in March and April, it became obvious that we can't proceed too far along without getting external input on this. And hence, this led to the idea of holding the two workshops which were recently held. And I'll tell you more about those.

So you might ask, why do we need this coordination at the HHS level? There are many reasons for these. From a public health perspective, I think this is an important public health issue and I think all of the HHS agencies are involved in public health efforts one way or another. The number of tests is increasing, especially of those categories that Francis had on his slide, those that are not diagnostic in nature but perhaps are testing for susceptibility or predisposition to disease. Commercialization is going on, obviously premature use, risk and benefit, et. cetera, et. cetera. I think the one before last is that the evaluation of tests does require longitudinal, clinical, and epidemiological data. To me, that is a very tricky part. And then the last step is that these data come from both public and private sources. So I thought these are enough reasons to justify that kind of coordination at the HHS level.

And what would be the goals for this effort? First, would be to work together with the private sector to identify the data elements that are important for each disease or each test; to explore a framework for how these data will be gathered, collected, massaged, and disseminated; and then developing an accumulated knowledge base which will change with time. As many people have mentioned, identify the gaps in the knowledge base. I think that is as important as the knowledge base, per se, because once you create those table shells and you find there is no data, I think an empty table reveals a lot of information, as much as a full table with stuff in it. And then lead on to the next step, which would be the facilitating of reviews of these kinds of data for a smoother transition from gene discovery to both clinical and public health practice.

So we held those two workshops. You had a summary of these in your packet yesterday. We had one on cystic fibrosis that Rod Howell chaired back on September 21st, and another one on hemochromatosis in October that Linda Bradley, from the Foundation of Blood Research, chaired. We wanted to limit the discussion to a relatively small group, not to inhibit discussion but to have a really working group framework. So we had researchers, consumers, health care providers, laboratorians, industry, and, obviously, the agencies involved in this discussion. We focused mostly on clinical utility and validity more than the analytic validity.

The way we started these workshops was very simple. We had basically staff people from my office scavenge the literature for available information, fitting stuff into tables. This is the simplest way to look at analytic validity from a genotype versus test perspective. Of course, this table has to be stratified by type of population, by ethnic group, by a number of factors, the populations have to be carefully defined, the tests have to be defined. There are all kinds of issues that go around that.

We tried to do the same with clinical validity in relation to phenotypes. We defined those phenotypes, we defined tests. And the two key concepts here that I think have been entertained before, are that when you talk about clinical validities, especially with respect to predictive ability, the clinical validity of a test becomes less of a characteristic of the test, per se, but more of the relationship between the gene and the disease, and the concepts of penetrance and heterogeneity emerge.

Let's take BRCA1 and breast cancer, as an example. The concept of penetrance is very important. Even if you have a test that measures the two or three or four or five mutations accurately with 100 percent power, the relationship between that positive test and the disease does depend on the penetrance of BRCA1 and it could vary from 10 to 90 percent depending on the setting. So it is really not a characteristic of the test primarily. And also heterogeneity, that reflects into sensitivity. If only 5 percent of all breast cancer is attributable to BRCA1, then the sensitivity of that test is going to be low, in the range of 5 percent, and it has nothing to do with the lab even if the lab does a marvelous job at picking this up.

And then clinical utility, we ventured very complicated tables as far as what the interventions might be. I don't want to share them with you because they are complicated. But it is really measuring the benefits of both positive and negative tests, and it really depends on available intervention after testing. In the case of cystic fibrosis, we talked a little bit about the impact of newborn screening, what would that do to growth parameters and pulmonary function. In the case of hemochromatosis, we talked about the impact of phlebotomy on the clinical outcomes.

Let me share with you very clearly at this point that, as a result of the effort, it was clear, at least to me, and Rod, you can jump in, and actually Elliott was on the discussion with cystic fibrosis, that by looking at available sources, be it published literature, test developers, lab data, web literature, et. cetera, that there is chaos out there. You construct your best 2x2 table and you go try to fill, you don't find it. The data might be available, but that is not the way people present it. Even the analytic validity, which I

don't want to dwell on it, people don't report stuff in that format. And Genzyme is the first to admit to that. Even on their web site you have detection rate, you don't know where the sample comes from. Actually, Elliott admitted this was not Genzyme data but data from the literature that they have scavenged from somebody else's data. So I think the real test is once groups decide what data you want and then you try to fill in the blanks, that's a real challenge that faces us.

So these are some of the possible sources of data collection that are obviously disease-specific. For example, disease registries are under special data collections which come in very handy, where the Cystic Fibrosis Foundation registry which captures more than 90 percent of CF cases in the United States. That may not be feasible for other diseases. We heard a little bit about the cancer model yesterday, but it has to be tailored by disease. Public health programs. For example, newborn screening for cystic fibrosis is done in four states and that is a very rich repository of data that will come in. And let's not forget the international sources because a lot of data especially on cystic fibrosis and hemochromatosis has come in from other than U.S. sources.

I just wanted to share with you this potential database for retrieval of information. There is a computerized retrieval of information on scientific projects which is maintained at the NIH. It is called CRISP. It is a repository of abstracts of all projects that are funded through all the federal agencies, not only NIH but includes CDC and HRSA and others. We found this as a very useful starting point to identify some of the projects that could lead to some information on clinical validity and utility for both hemochromatosis and cystic fibrosis. Again, these are government-funded projects which we could use to target the investigators to get more data to fill those tables.

In terms of methods of dissemination and synthesis, we talked about a number of models that exist out there. Some of them vary from expert panel, an expert person writing a chapter, like with gene clinics, which is the Bonnie Pagan model, the gene test is basically a repository of labs that perform testing and we use it heavily, but we couldn't fill in the blanks with the data we wanted from these two sources.

The second source is the U.S. Preventive Services Task Force, which is under the auspices of AHCPR, and David Lanier has just disappeared. It is a very useful model because this uses evidence-based medicine to synthesize data from different sources to come up with recommendations that are fairly specific. For example, does aspirin reduce the risk of MI, or does chiropractic help for low back pain, which happens to be an ailment of mine.

Then this Cochrane Collaboration is a third effort which is a worldwide group, primarily academicians, that review/synthesize information, and they've really done a wonderful job. I met with their executive committee a few months ago. They're interested in clinical utility information. They're not particularly interested in clinical validity stuff. They want to know based on controlled clinical trials whether agent A reduces disease B, or whatever.

Then of course the last one, which is sort of my own pet thing, is the Human Genome Epidemiology Network, which is a global collaboration that we started with a number of organizations and people to basically disseminate epidemiologic information on human genes. We have a web site. I don't want to dwell too much on that.

The synopsis of the two data workshop recommendations. Basically, that both groups endorsed the idea that this is doable if you get groups of people together around cystic fibrosis and hemochromatosis, the experts in the field, they can define, with input from consumers and a number of groups, what the data elements are. They know their subject matter more than I do or anybody does. There was more of a quick consensus around CF. Basically within the first hour we got there. With

hemochromatosis, it took almost half a day to get there. Primarily, the chemistry of that group was a little bit different. The private sector representation was very different, the hemochromatosis testing is now in flux, it has changed hands at least two times over the last year, and the kinds of data that are available are more tricky and it is more recent.

So what we're trying to do in the next year or so is conduct feasibility studies that will be coordinated by CDC and our Interagency Group to develop pilot studies around these efforts. The areas of emphasis that the groups have identified for CF: Obviously, newborn screening, carrier testing, and then the third area, which is a very important area, is expanding the phenotypic definition of cystic fibrosis. So, what's the relationship between CFTR and chronic sinusitis, or male infertility, or some of these other lesser endpoints. Around hemochromatosis, the three areas of emphasis will be: Population testing, clinical diagnosis, and then family studies where you use a genetic test in a particular family study.

So now what I want to end up with is an overall framework for how I see -- next slide, please -- the framework as independent of whatever regulatory paradigms that this group will come up with. The regulatory paradigms will be at FDA, or CLIA, or all of the above.

Basically, the shell or the environment under which such an effort could operate -- and this could essentially run in parallel or completely independent of any regulatory paradigm -- obviously, there has to be some oversight of this process because you can think a hundred thousand genes, a few thousand tests at a time, you can't do this fairly quickly. You have to decide which ones you want to tackle first before you get too far.

And then the model would the Working Group model of experts in the field that are disease/test-specific, with adequate stakeholder representation. That essentially will create the kind of framework, the types of data and the data formats for which we want to collect those data. And then with some help and coordination from HHS and CDC, we will go gather the data for them and then we will throw it back in their lap.

We discussed at length options for data synthesis and dissemination. Who should have access to the information; the model of a static versus a continuous flow, because after this group will make an initial cut on reviewing this data, more data will be coming in and will be collected for future evaluation.

We talked about options for how are we going to collect the data. Will it be in aggregate format versus individual patient issues. Issues of confidentiality came up, obviously. We want to balance the issue of whether we keep this kind of data in a centralized place or decentralized, whether this would be owned by the researchers or the test developers. We want to define some quality control parameters around which data is good and which data are not as good. Obviously, we want to expand and build on what other groups are doing; there is no sense reinventing the wheel in some areas where there are existing consortia that we can immediately plug into.

What I am hoping is that in the next few month we will implement those two pilot projects, cystic fibrosis and hemochromatosis, as a way basically to test the feasibility of this approach, to test whether or not there will be participation in this kind of effort.

So the bottom line in my mind is that for many tests data are not available, for some tests there is a lot of data out there but it may be chaotic, disorganized, not in the right format, not reviewed in a systematic way. And for both of these there is a process by which we can essentially create the framework by which those data can be collected. And if that framework is adopted, then it could be the basis for future data collection efforts and will help facilitate the review process of each test.

And if I haven't said it, I think I should have, a lot of the published literature doesn't have what you want. That, to me, is a clear thing. I may have said it at the beginning. And if they have it, they may not have it in the kind of format that you want. So there will be some more labor intensive effort to do this. But both groups said it is doable. And I think that we heard it clearly from the cystic fibrosis group. The hemochromatosis group said, well, let's do it and see what we get.

Thank you.

DR. McCABE: So Muin, I take it then that you are going to have these groups begin to collect these data or design a format for capturing these data.

DR. KHOURY: Yes. I think the next step would be, we have an Interagency Working Group discussion next week, sort of a postmortem to these meetings. All the HHS agencies obviously have to review this and some of them around the table have not actually heard this but their operatives have. So we want to get feedback from within HHS. I think there is commitment within CDC to go ahead and do something like this and evaluate how feasible it is, how much money it will cost.

And there are all these logistics because you think about this effort on case-by-case basis. I heard some basic estimates for this that in order to do this, each one of these efforts is probably about a $200,000 affair. It will take probably an infrastructure of probably somewhere $500,000 and $1 million per year to keep it going. And these are the estimates I got from the U.S. Preventive Services Task Force and some other groups as well. Because what the process will entail is reconvening groups, let them work on the kinds of data they want, and then basically go try to collect that information with their buy-in so it doesn't become a government-driven effort but is something that would be useful for the community and by the community.

DR. McCABE: But that's per disease? You're talking about $500,000 to $1 million a year infrastructure plus $200,000 for each disease?

DR. KHOURY: These are very rough estimates. It's still pretty much lots of money.

DR. McCABE: Lots of diseases.

DR. KHOURY: Yes.

DR. McCABE: Elliott?

MR. HILLBACK: Yes, I'd just like to comment, having been at the meeting, I was very privileged to be there, I thought it was a very exciting meeting, we do have some advantage with CF in that we're really doing a retrospective look at a lot of data that already exists. And we have the advantage that the CF Foundation has been the leader in creating these CF centers and they have a lot of phenotypic data that is available.

For the luck of the draw, we have become a very large testing lab and have, therefore, tested a lot of those same CF patients. So with one lab and a group of CF centers, I forget now how many there are, we have we believe an incredible genotype phenotype overlap that we can bring together rather rapidly. The cost will be relatively higher in one sense in that we're going to put a lot of data together that is retrospective that has been created over ten years.

So one of the other issues going forward, if you started afresh with a new disease, a test that's being launched, you don't have that big bollus at the front end, you also don't, unfortunately, have the

promise of a fair bit of useful information pretty rapidly, which we think we have with CF. But it's an interesting experiment and we're very much supportive of it and are going to put a lot of work in at Genzyme.

DR. McCABE: Wylie?

DR. BURKE: I think to the extent that we take seriously the idea that clinical validity and clinical utility are key pieces of information to have about a test, that this is a very important model, really an essential kind of process to ensure that we have the information. It seems to me that as we go forward exploring this kind of model, one of the great advantages that we may be creating is that the model will begin to create or set standards for data formats. And I think as standards are set for data formats, we may see a very positive development over time that it will influence how data is recorded and maybe even how data is gathered so that over time some of the real difficulties that you've had in terms of getting hold of data may be solved.

I think, too, that setting a standardized data format really creates the discipline that is essential for some of the difficult problems. I'm sure that you in the hemochromatosis workshop found that one of the difficulties is lack of agreement on what a case definition is. You certainly can't answer a question about clinical validity until you know what the case definition is.

The two other comments that I would say are, that I think this model is likely to be particularly useful if it is constructed to be independent of the regulatory mechanism. In other words, if it is seen as an independent source of information that doesn't have an agenda but in fact is a reliable objective source of data collation and evaluation that then is available to all people, all interested parties. And obviously, you alluded to it, that leads to I think tremendous attention needing to be paid to how the information from such process is communicated.

DR. McCABE: Pat? Why don't you join us and broaden the discussion.

DR. KHOURY: Yes, thank you.

DR. CHARACHE: First, to clarify definitions. I'm hearing the simplified definition of clinical validity as the predictive values, negative and positive, for the presence or absence of a gene or genome, and that clinical utility is defined as the predictive value for the presence or absence in the future or now of a disease state.

DR. BURKE: No, I actually think we're talking about clinical validity as predictive value for phenotype.

DR. CHARACHE: That's clinical utility.

DR. BURKE: No, clinical utility incorporates interventions to improve outcome.

DR. CHARACHE: Okay.

DR. KHOURY: No, the clinical validity slide showed the relationship between the test and the phenotype. The phenotype could be a disease or it could be a quantitative measure, like iron stores in your body.

DR. CHARACHE: Okay, great. Then having said that then, using that as a definition of clinical validity, I think it would be very helpful to define very early on, right away, what parameters are going to

be required to say that a test has clinical validity so that enforcement can be based upon such. We have some ideas, but I think your consortium should see them and address them so that we need not wait to use those criteria for saying that a test is ready to be launched.

DR. BURKE: And that's an example of the value of a standard-setting process.

DR. CHARACHE: Excellent.

DR. McCABE: Pat?

MS. BARR: I had two thoughts. One is, is it possible to create a working group without a disease but with a type of test? And the other question is, since it was an ELSI task force that talked about needing to validate clinical utility and clinical validity, and there is ELSI money part of your budget every year, is it reasonable to look to your agency as well for funding for these kinds of efforts, because it is the core of some of the ethics of doing it.

DR. McCABE: Francis, I'll let you respond to that since the question was directed to you and your institute.

DR. COLLINS: It's not out of the question. It would be critical though to see how this fits in with the ELSI program's congressional mandate, which is to do research on the ethical, legal, and social implications. And to the extent that this is research, that fits. To the extent that it is part of the regulatory process, it doesn't.

DR. McCABE: But I think what we heard from Wylie was that there is some advantage of keeping the research separate from the regulatory process, which, again, having your institute involved with being non-regulatory, NHGRI would certainly diffuse that concern to some extent.

DR. COLLINS: Yes.

DR. McCABE: I'm wondering if we could ask you perhaps, Francis, to have your staff research that and see if it would fit. Because I think Pat's point is that getting these data are critical to the ethical practice of genetics.

DR. KHOURY: In order for this to work, I think all the federal agencies have to band together. Because, for example, HRSA will have a tremendous role in this effort especially around newborn screening where data are being collected, CDC with its surveillance systems will have a role, AHCPR with its evidence-based centers. So the thought sort of an interagency group is very important.

DR. McCABE: No, I understand that. But I think there was also the issue of if this is done at a research base, that if you have to set up one of these task forces for each disease, that is going to be very difficult. If there was some investigator-initiated funding -- if you set up the model and then other investigators wished to pursue it with additional diseases based on the interagency model, that there might be some benefit.

Francis?

DR. COLLINS: Yes, I think we should think broadly about models and not assume that one which is heavily represented by agency folks is necessarily the ideal. I would be interested in knowing for the hemochromatosis example, or for the CF example, since there have been groups that have looked at both of those -- maybe take the CF because, after all, ACOG and ACMG have been engaged over the course of the last two years in trying to come up with an implementation plan for the NIH consensus

development workshop recommendations about CF carrier screening being offered to high risk couples; that is, couples from populations where the frequency of CF is fairly high.

What was different about your deliberative process compared to the NIH consensus development conference, on the one hand, and the more implementation-based ACOG and ACMG enterprise? And what about the model that you just described added value that wasn't available in other --

DR. KHOURY: It's very simple. Actually, we started with the basic premise that this work is not designed to either do consensus -- it is not a consensus statement. We wanted to start from the top and use actually all the information that has been gathered through these workshops and some other means and we wanted the group to decide which data are important and let's see whether it exists. I think when you start from the top and you decide the kinds of data that you think are important and then you try to collect it, you would be amazed, Francis, that sometimes you think the data might be there but you don't find it, or if it is there it's not displayed in the right way that your consortium has come up with.

So I see this effort as preceding or leading up to consensus conferences or workshops or meta analyses. I view it as an integral part of the process of helping these groups. And forget about CF for a moment, but pick a new disease, a new gene, and I think if we train ourselves to be kind of disciplined to create the knowledge that we think are important, and the we is a collective we, it is based on the input of researchers and consumers and public health officials and the whole thing, then you try to collect that data and it becomes a framework for future data collection if the data doesn't exist. So it's basically a process more than a snapshot in time whether we're ready to screen for cystic fibrosis or not.

DR. McCABE: Wylie, then Pat.

DR. BURKE: I just wanted to add to that. I think what we're really seeing as we hear this process described is the need for some explicit support, whether through agency activity or through extramural funding, for a process of secondary analysis. I think the model we're often used to dealing with is that there is a series of papers that provide primary data, they've often attacked the problem in a variety of different ways, they've therefore collected data that isn't fully comparable with each other, and then we bring together a conference to make sense of that data.

But often there is a need for an analysis process to get the greatest value out of those disparate pieces of primary data. And that process of secondary analysis often has to start with a definition of terms and figuring out what data is comparable and what data is not comparable. And I actually think one mechanism might be to think about providing additional support for that kind of process through regular research funding.

DR. McCABE: Pat, and then we're going to broaden this out and move away from Muin's presentation back to question 4.

MS. BARR: I guess the first question I had wasn't answered. I understand Wylie's point that if we do it for a number of diseases, through that we may get standards. I guess my question was, given that what you really hope for is the dataset when the test comes out, is there a way, or have you thought about a way to get groups together who could think about the dataset from the beginning for the labs?

DR. KHOURY: I guess the thinking has gone on. I think the problem though, Pat, was that we were faced with the immensity of the situation. We created empty table shelves with things as vague as genotype and phenotype and intervention and it became quickly apparent, and outcomes, a number of outcomes, but it became quickly apparent that most of these things are disease and/or test-specific. And the complexity of CF and hemochromatosis illustrated really the opposite end of the spectrum with respect to the diseases.

I think you can create a generic model that you would hope that people will adopt. But in order to implement it, it will have to be more disease-specific. That is where the expertise lies and that is where the data comes from. Because the CF people don't talk to the hemochromatosis people, and vice versa.

MS. BARR: That's why I was asking about a generic model.

DR. McCABE: Barbara, very briefly, and then we've got to move on.

DR. KOENIG: Just a very brief comment on this area. It is my understanding, and I don't know much about this, but that phenotype genotype databases or sets of information are in themselves becoming important commodities which are perhaps bought and sold. I am just wondering how that as a phenomenon in and of itself, taking heed of Professor Buchanan's warning yesterday that we shouldn't start with a presumption that's not appropriate, but how does that fit into this?

DR. KHOURY: It does, and actually this came up especially with the CF discussion where there are consortia around genotype-phenotype correlation that Gary Cutting, for example, from Hopkins is involved with with Toronto and other groups, and these groups will be brought to the table. The only caveat there is that these kinds of collections are not representative or epidemiologically kosher, so they will have to be a little bit more massaged. But the idea is there. I think consortia, some of them will work more than others. I think with CF we're already on our way.

DR. McCABE: Well, we're aware that there are these proprietary databases that are being developed especially in the pharmacogenetic area.

Let's move back then to the more general discussion of question 4 just for 10 or 15 minutes, and then we will move on to the conceptual questions regarding oversight.

I'll just make a statement that I found that the presentation of 4A and 4B I think helped with some of the discussions on 3 in point of fact. So that I think that's very useful to have included in the document. I almost wonder if it's a little bit out of order as I was thinking about it because I think that some of our discussion this morning really would have been informed by having 4A and 4B come before 3.

So we may want to rethink in the document the order of these. We would have to look back, but, if not, then maybe they need to be somehow together. But what we were really talking about was some of the premarketing stuff and some of the tests going from the research bench to the clinical laboratory was at least what I took away from some of that discussion. So as we're recasting it, we can think about it. Maybe it's fine where it is and one just needs to look at it as a whole.

Other discussions of 4A and 4B then?

Yes, Pat?

MS. BARR: I have a question. You talked about earlier the pediatric oncology model where you had a tremendous amount of cooperation I believe. And we talked abut the cancer registries where, indeed, the patients themselves don't necessarily know information is going into a registry. And there has been a tremendous amount of concern about privacy for genetic testing information. Would it be useful, and this is a question, to somewhere in the document let people know that data is collected already for certain kinds of situations and that it has been helpful, and then to also ask people the question of the trade-off of some privacy versus research and data collection. Because that is one of the political issues

we will have to face over time.

DR. McCABE: Yes. First of all, I thought it was helpful when Dr. Howell went through the different types of consortium -- cancer, the neonatal network, and the PKU collaborative studies. Each of them is a little bit different, but I thought that was helpful.

My understanding, I'm not an oncologist, but my understanding of the difficulties in the cancer is the going back in and mining those data. The patients are informed up front and have informed consent for the protocols, at least in the pediatric community they do.

MS. BARR: Oh, yes, for pediatrics.

DR. McCABE: The pediatric oncology protocols are very extensive.

MS. BARR: But not in the public health registries.

DR. McCABE: Right. But then the issue having to do with the consent issues has to do with then these data going into a database and that being remined and looked at in various different ways without reconsent.

Yes, Dr. Feigal?

DR. FEIGAL: If I could just comment. I think the one thing about many of those consortium were that they were organized groups of investigators who dedicated a large part of their academic career for decades to those groups. And there are other interesting examples, too. There is the UNOS transplant registry that has every transplanted organ in the United States in that database. But also many of these have been marshalled around intervention trials. And there is a lot more enthusiasm for that than getting investigators together to learn about natural history.

So I think that if this is something we think is really important, it's going to take some time to build consensus and get the logistics for that going. And what has been successful in pediatrics, where you have almost all the children in it, it doesn't work very well in adults where you get less than 10 percent in trials and you have trials that close for lack of enrollment. So there is a lot of differences in the psychology of different diseases, having interventions, having successes, which you have more of those in pediatric oncology than you do in adult oncology.

But I think there probably isn't a single model. But the theme that to me cuts across all of them is you have got a group of investigators who are willing to get together nationally as a consortium of some sort and work on a problem over a multiyear process. I don't think there's any passive system that is just going to magically have the stuff there and then people will mine out. That's sort of what the National Center for Health Statistics is. They have data that goes begging for analysis because their own staff doesn't have enough time to analyze things, like the health and nutrition surveys that they collect, and they have trouble getting people to look at all the things they collect.

DR. McCABE: Pat, I'm not sure if we answered your question.

MS. BARR: No. My question really, and I probably framed it with the wrong models, but there are registries that peoples' data is going to, they don't know it's going there. Those registries are useful for making certain kinds of epidemiological determinations. But the public doesn't know it's happening. And now there is a tremendous pressure that every time anything moves there is a long and arduous consent process.

So it seems to me that one of the questions we might want to ask the public in our outreach, if it's appropriate, it may be opening a can of worms, is how they feel about the trade-off of giving up some privacy in favor of the collection of data that will be useful in the long run.

DR. McCABE: I think that's very important and we probably should build this into the document so that we can get some feedback on oversight on this and discuss some of the consent issue.

Judy?

DR. LEWIS: And the other piece of data that I think we need to think about collecting, in addition to those that Kate mentioned, is some kind of how did this make a difference, what worked, what didn't work; some kind of consumer satisfaction data or some kind of QA from the perspective of the consumer so that we're able to talk to people about what worked about the process, what didn't work.

MS. BARR: We know what happened.

DR. LEWIS: I'm talking about the data collection methods that we looked at. This isn't directly in reference to what you were saying, Pat, but in terms of some of the data that we need to collect I think needs to be some kind of consumer utility, for lack of a better term.

DR. McCABE: I think that part of why people will tolerate this in some of the other areas, first, there's not the sensitivity there is about the genetic issues and the impact on relatives. But secondly, I think it gets back to the issue of intervention. If your data are being used to improve the care of other individuals, somehow it seems more appropriate than when it is just being used for diagnosis. And so that I think the concept of the tie to intervention is a very important concept for public participation in these things too.

DR. McCABE: Joann, and then Barbara, did you have --

DR. KOENIG: Just a quick comment.

DR. McCABE: And Reed. So Joann, Barbara, and Reed.

DR. BOUGHMAN: There are two or three other issues that I think we need to keep in mind as we step back from this. First of all, not only does the cancer or even the newborn registry fit the medical model, it fits a disease model. And we've been trying to move away from that to some extent.

Also, once we cross the line into the world of genetics, we have to ask the question are we looking at retrospective data. Because in the cancer registry, we've got the cancer patient. That's not the issue anymore. And in genetics we may be talking about a test result that is predictive and we don't even know exactly what all it could be predictive of.

So, in some respects, these are very different worlds. And if we're going to ask some of the questions, we need to frame them in such a way that we're going to get the answers to the questions that we really want answers to.

DR. KHOURY: Can I comment on that, because this is directly related to her question.

DR. McCABE: Okay. Very quickly.

DR. KHOURY: I have a paper coming out in the next few months on how we can actually use

population-based registries that are epidemiologically defined retrospectively through case-controlled studies to estimate penetrance of genotypes easily. Because you have through the C registries, for example, you have incidence rates that are yearly and you can do a case-controlled study and come up with a few assumptions, a more prospective look at things using just a few assumptions. So let's not discount the retrospective way of looking at data in addition. Obviously, the prospective way to look is the gold standard. But there are other creative ways to do this.

DR. McCABE: Barbara, then Reed.

DR. KOENIG: Just very quickly, I want to follow up on what Pat Barr said about the issue of what we should actually be asking the public's views on. One of the trade-offs that is necessary to get the data that we need is the trade-off between privacy and individual choice about being put in registries. And another one that is related to it and which is very much related to the key clinical transition that we're talking about, which is the transition from research into clinical use, is what level of trade-off are people willing to make in terms of not getting access to results early on when there's not much known about the clinical validity and utility of the test. And I think that's another thing. If we decide to frame some of the questions in terms of sort of the global macro level questions of what we're asking the public to trade off rather than about the specific oversight questions, then that's another one I would like to see discussed.

DR. McCABE: Reed?

DR. TUCKSON: Yes. First of all, I think it is an exceedingly important question. I think the fun and the challenge will be also how we present the benefits of the data to the public. You can almost sort of see this would be a self-fulfilling prophecy, that once you put it on the table, there is almost no way that I can imagine the public would consent to very much in the way of trade-off of privacy and confidentiality for the sake of a very abstract benefit, a benefit that we would even have a hard time articulating to many researchers much less to the public themselves.

I think there is no way, Pat, you've actually put us on the horns of a pretty good dilemma, because once having raised it, there is almost no way we cannot deal with it. I went back again and just reread the charge. So once you put it on the table, you can't take it off. So I think it's important to do it.

MS. BARR: Maybe we can if Muin thinks he can do it without.

DR. TUCKSON: But I do think that the skill set will be how we articulate the benefits, and then what we decide to do with the answers that we get.

DR. McCABE: Pat?

DR. CHARACHE: Just pursuing the train of thought that's on the table. I think that as the document goes out for public comment, it shouldn't be presented only as a black and white, but with options within that, such as what degree of privacy would permit your data to be shared.

DR. TUCKSON: That's helpful.

DR. McCABE: I want to transition now and move on to the next. But before I do, I want to talk a little bit about process. We have a document. We have been discussing over the last day and a-half some significant revisions to that document. We don't have another meeting scheduled before our public consultation and we've got to get the consultation document out.

I'm wondering if you would empower a very small writing group -- which I've already talked to Kate, and it would be basically Kate, Sarah, and I -- to try and take the notes that we've been taking

through the meeting and the discussion and put those into the document. If people have specific things that you've talked about and would like to see in there, you can certainly e-mail them to Sarah and we'll try and put that together over the next couple of weeks. We will try and have a conference call of the Oversight Working Group on this document, may have to bring in some others, to try and get this done so we can have it out for the November 15th deadline. Is that acceptable to everyone?

Excuse me?

MS. BARR: Do we have a November 9th call also?

DR. McCABE: Yes, we have a November 9th call. Yes, we could even try and have it before then. Yes, we did have a November 9th call because we had planned a meeting. But I think that part of what I'm saying in this, embedded in my statement is that we will take what we've discussed here and not go beyond what we've discussed here because we've discussed this in a public forum. To go beyond what we've discussed in the public forum would require another public meeting and we really don't have the opportunity to do that.

Francis?

DR. COLLINS: Can I also ask, since we're talking about process, this document is full of information but it's not very user-friendly. I suspect if it is the sole way in which we seek public comment, we'll see a lot of glazed eyes. So can you clarify what is a more easily understood version of this, Elliott I think was talking about this issue this morning, where you have a series of specific issues that one can easily get one's mind around and the public can figure out, oh, that's what they want to know. Because it isn't entirely clear from the more encyclopedic document.

DR. McCABE: Yes. We are going to develop, in essence, an executive summary in both English and in Spanish. We can take note of your comment and really frame the issues much more carefully there so the issues are much clearer.

DR. COLLINS: Yes. Not only an executive summary that sort of distills or abstracts what's in here, but makes it really clear what are the areas where input is specifically being sought.

DR. McCABE: Okay.

DR. TUCKSON: I wonder, and I don't remember our resources, but do we have the opportunity or maybe the time to have an editor-type person who is a like normal human being-type person.

(Laughter.)

DR. TUCKSON: Because I think that what we're not talking so much about here is the synopsizing it down to a summary, but really sort of saying in language that the "average person" can understand this is what we're really asking you.

DR. COLLINS: Right.

DR. McCABE: We do have a science writer assigned. I just asked her if she fit the definition of a normal human being.

(Laughter.)

DR. COLLINS: And the answer is?

(Laughter.)

DR. McCABE: But I think that with the charge, she was given a very complex document and it is much less dense than it was before. I think with the charge that she's just been given, she can try and make it even more appropriate to the audience for which it's intended.

DR. COLLINS: Can I also then make a plea that if there's another conference call to look at the latest version of the big document, that the smaller document, which in many ways is the thing the public is really going to attach themselves to, also gets reviewed by that group.

DR. McCABE: Yes. There was a version of that that was sent last week.

DR. COLLINS: A five-pager. I still think that's really more of an executive summary than what Reed is talking about, which is a bit more definition of the issues that we want people to respond to.

DR. McCABE: So we really need to frame the issues. Okay.

DR. LEWIS: So is this something all of us are going to get a chance to respond to and review before it goes out?

DR. McCABE: What we will try and do --

DR. LEWIS: Or is it just the one working group? Because I think part of what happens is that when people are so close to something, the people who haven't been so close to it sometimes can have a different perspective that might be a little bit more --

DR. McCABE: What we can try and do is have it for the November 9th. Is that doable?

DR. TUCKSON: Ed, by the way, in the interest of time, I just want to say that the document, the people that have been writing it are wonderful. I love what's happening here. I didn't mean any criticism.

DR. McCABE: Yes, Joann?

DR. BOUGHMAN: I had suggested at one point fairly late in our writing that we actually went back and extracted those statements that ended with a question mark and add in almost a list or a nested kind of thing under the various questions. Then there were a couple of responses to that, that that was getting more to what Francis was pointing out. On the other hand, from our conversation this morning, it seems like we may be backing away from the four-issue format and really kind of tossing the deck of cards up in the air and reshuffling them. Am I hearing that correctly?

DR. McCABE: I'm sorry?

DR. BOUGHMAN: That from this morning's discussion that we were backing away from the four issues and the tables as presented.

DR. McCABE: No, I think we'll still have the four questions, the four major questions.

DR. BOUGHMAN: Okay.

DR. McCABE: But what Sarah and I were just discussing, what I hear as a mandate from the committee is that we now frame the subquestions underneath those four questions. What are the issues,

and we need to do that in either bullet form for the issues, or where there are questions that we want specific feedback from the public, that we frame those as questions. But we also need, I think I heard yesterday more than today, that we need to have some open-ended questions and some additional questions not encompassed by those four major questions that were laid down by the Surgeon General and then remassaged by us earlier on and by the agencies. Is that what we're hearing?

And in terms of who will hear this, if we can have it for the November 9th date, then that will be a conference call of the group. But again, I'll make it clear that what we're going to do is take what we have heard here and not go beyond what we have heard here.

Yes, Wylie?

DR. BURKE: And just as a sort of minor comment on that. I really think this executive summary that needs, as we've said, to become user-friendly should have a very visible and tight correlation between small sections of explanation and highlighted direct questions, the bullets or the boxes.

DR. McCABE: Yes. I think what we'll do is we'll take what we had before plus what we've heard in the last two days and try and make it more bullet. A lot of that will have to do with formatting as well.

Sarah, do you feel like you're comfortable? Okay. Okay.

Now I'd like to move on to some of the conceptual questions, a lot of which we've been dealing with as we've been going really. But I want to go back over them and sort of review them in the next twenty, twenty-five minutes.

So the conceptual questions that were laid out, there were four of them, and I'm going to read through all four because I think that it's important to see the group before we get into the individuals.

Given the complexity of the factors to be considered in assessing risks and benefits of genetic tests, is the assignment of tests to distinct risk categories a reasonable goal? So that was the first conceptual.

Are the distinctions between clinical validity and clinical utility important with respect to oversight?

Can oversight be flexible enough to response to rapid advances in knowledge of genetics?

Are additional or different oversight options needed to address genetic tests that have significant social implications?

So let's go back through these one by one. Given the complexity of the factors to be considered in assessing risks and benefits of genetic tests, is the assignment of tests to distinct categories a reasonable goal? There is the discussion, some of which falls out of the task force, a bit embellished by us, in terms of what are the high-risk, low-risk categories. They are summarized in the document in terms of high-risk, low-risk, and potential-risk, and potential benefits in those categories.

Does the committee feel that this is a useful construct?

Yes, Pat?

DR. CHARACHE: I think in terms of regulatory activities, it would be very helpful to have such a categorization. I can see problems in getting such tests into categories as a delaying factor to implementation. But I think that it probably should be worked out that it can be done.

DR. McCABE: Muin?

DR. KHOURY: Just in terms of non-regulatory data collective perspective, I think it is also important because you have to prioritize how many tests can you collect data on in any particular year. In any intensive sort of a model I presented earlier, you really have to categorize. At least my conception of this is if you end up with a dichotomy of high versus low, the majority would fall under low and only a few would fall under high. I could be wrong on that.

DR. McCABE: Yes, I think that it gets back to Pat Barr's issue before in a way, that right now we're dealing with disease-specific issues. We can't deal with a thousand disease-specific issues. But if we begin to develop some conceptualization of the issues around low-risk and high-risk, recognizing that we may change the definitions, we may change categorizations and have subcategories, or a third category or whatever as we develop experience, that that will allow us to expand to the rapidly growing group of diseases. But if each one has to be dealt with uniquely, it's going to be very, very difficult.

Joann, and then Judy.

DR. BOUGHMAN: I simply would like to state I have a problem with the term "distinct" because I don't think we're going to ever achieve distinct. We may achieve arbitrary categories, but probably not distinct ones.

DR. McCABE: That's an easy editorial change. We've removed "distinct."

(Laughter.)
DR. McCABE: Judy?

MS. YOST: Just a thought. If we're going to prioritize by risk, clearly you have all explained that there are often genes that are identified that may affect in some way maybe a very small population of individuals. I think you also might want to balance with frequency or size or number of population that is affected by a particular test.

DR. McCABE: Judy Lewis, and then Pat.

DR. LEWIS: And another parameter I think we need to look at is time, because I think things can move from category to category over time as we get more knowledge. So I think we need to keep the time parameter and not categorize things on a long term basis.

DR. McCABE: And we certainly have an example of that, not moving from one category from another, but certainly where the way we deal with it is very different now than it was two or three years ago, and that is Huntington Disease. The pre-analytic phase of Huntington Disease has gone from six months of very formalized process and counselling and education down in most centers to still involving education and counselling but not of the same duration.

Yes, Pat?

DR. CHARACHE: I would like to separate disease prevalence from risk category. Just because

only a few people are heavily involved, I don't think it changes the risk category. If we have a generic definition that describes a risk category, then any disease should be able to fit into it whether or not it's high or low prevalence as you categorize it. What you do with it might differ by prevalence.

DR. McCABE: Francis?

DR. COLLINS: I think as a practical matter, though, when it comes to risk, we're talking about risk to the population. Prevalence is going to kick in, and realistically, we probably can't put the same resources into evaluating a test that carries a certain risk to a handful of people as compared to something that might be offered to the entire population because it's much higher in its prevalence.

DR. CHARACHE: No, I think what you do and how you assign your resources or what your requirements are in the lab can vary, but it doesn't change what the risk is to a given population that happens to have that disorder.

DR. COLLINS: I guess we're sort of hung up on a semantic issue here. I agree with you. It doesn't change the risk to the individual, but from the point of view of the application of tests to the population and where the attention ought to be the strongest, it certainly has an influence on that.

DR. CHARACHE: Yes. I have no problem with that.

DR. McCABE: As we've been talking, I've been thinking back to the issue about the documents and the details of the documents, and I'd like to make a proposal. The executive summary I think was really very good and is an excellent executive summary of the longer, more dense document. I would like not to throw that out, and as we redo the document, we will retain that as an executive summary, but then we will go through, and with a similar format and outline, then frame questions, so that in fact we will end up with three documents, but we will be having one that is more targeted to our public consultation and addressing issues that we would like feedback on in that.

Is that acceptable, Joann?

DR. BOUGHMAN: Not only is that acceptable, but if they are separated somewhat on the Web site, so that people could get directly to the questions for feedback and not have to go through the 50 screens or whatever of documentation prior to getting to the questions, it would be helpful.

DR. McCABE: Okay, and then I had Victor and Pat.

DR. PENCHASZADEH: Pat?

DR. CHARACHE: Excuse me. Would the content of the current executive summary for Section 3 be the same and the order the same?

DR. McCABE: We need to look back at that and see. Probably. We need to look and see if we need to flip it. We will take into consideration the discussion as we alter the document and the executive summary, but I don't want to throw out the executive summary.

Yes, Victor?

DR. PENCHASZADEH: To clarify the question, for these first questions, I think we are all agreed that there should be these different categories based on risks and benefits, although I admit sometimes it will be difficult to define which goes where. So there will be some degree of arbitrary decision.

But I probably think that the term "risk categories" might not be the most appropriate, because risk is a relatively subjective concept, and it may be confusing. It's not simply the risk of something occurring, but it's the severity, it's the availability of treatment, it's the prevalence, it's the clinical population involved, and so on and so forth. We may want to think of another term, like "importance" or "priorities."

I don't know. I have a problem in --

DR. McCABE: Well, we can -- yes, Wylie?

DR. BURKE: I'll just offer a brief semantic solution to that. I think we can just talk about different oversight categories, sort of more intense, less intense, and that may permit us to capture the issue of prevalence for orphan diseases in particular.

DR. McCABE: Right. So we will change this first question, then. "Given the complexity of the factors to be considered in assessing risks and benefits of genetic disease, is the assignment of tests to oversight categories a reasonable goal?" And what I'm hearing is that we've agreed on that.

Number 2, "Are the distinctions between clinical validity and clinical utility important with respect to oversight?"

Yes, Wylie?

DR. BURKE: We actually haven't discussed Dr. Kang's from HCFA statement, but I thought it was very interesting and very pertinent to this question, in which he proposed that tests that had clinical validity, but not any proven clinical utility might be ones that would be appropriate for certain kinds of delivery, for one-on-one service, for patients autonomously choosing to be tested, but might, for example, not be appropriate for the use of testing in a universal screening situation, and I think that came up in public health, too.

So I think there's no question that we have heard discussion that says there are times when proven clinical utility is a crucial piece of information and possibly times when it's not. So I think we've already sort of had the discussion that says we need to keep thinking about those two different categories.

DR. McCABE: Michele, did you have something? I thought I saw a hand up over there.

Muin, did you want to say something?

DR. KHOURY: I'm just agreeing with Wylie.

DR. McCABE: Okay. So basically, the discussion of the last day and a half says that it's important to have those, and we will retain that worded as is.

"Can oversight be flexible enough to respond to rapid advances in the knowledge of genetics?"

MR. HILLBACK: The answer is it has to be.

DR. McCABE: So I think that one of the concerns, then, is that perhaps it isn't right now, but we have to be creative and figure out ways that it will be.

Pat?

DR. CHARACHE: I was just agreeing with that. There's no other option.

DR. McCABE: Joann?

DR. BOUGHMAN: Maybe we could reword, then, and challenge ourselves and the public by saying, "How can oversight be made flexible enough to."

DR. KHOURY: Actually, another way to be even more proactive would be "How can oversight" -- I forgot the word.

DR. McCABE: Okay. So "How can oversight be flexible enough" --

DR. BOUGHMAN: "Be made flexible enough."

DR. McCABE: "Be made flexible enough to respond to rapid advances in the knowledge of genetics."

DR. KHOURY: Okay, the word is, instead of being passive, "respond," but to actually be more active, like "use" or "incorporate" or "utilize."

DR. LEWIS: "Streamline."

DR. KHOURY: Because we know that advances in knowledge are happening, and oversight has to be creative enough to be able to use that in some creative fashion.

DR. McCABE: So "to utilize the rapid advances"?

PARTICIPANT: Or "incorporate."

DR. KHOURY: "Incorporate."

DR. McCABE: "To incorporate," okay.

MS. BARR: How about "incorporate and respond"?

DR. CHARACHE: No, it's both. Respond is incorporate.

MR. HILLBACK: But oversight isn't incorporating --

DR. McCABE: So "respond and incorporate" or "incorporate and respond"? "Incorporate and respond," okay.

DR. LLOYD-PURYEAR: Can I ask --

DR. McCABE: Yes, Michele?

DR. LLOYD-PURYEAR: Is that because we're envisioning a system that the test is really -- it's this first question that you said, when is a test ready for prime time? I mean, right now, you have premarketing and then you market it, and sort of the postmarketing is the adverse events or just other things that may happen, but that's with other tests.

But with this, you're going to be doing your postmarketing in your marketing, and that's where you're going to be acquiring your clinical validity and clinical utility knowledge, and so you're imagining an oversight system that's constantly evolving.

DR. McCABE: Right, right.

DR. LLOYD-PURYEAR: And so utilizing the information that's coming in, and then responding to it.

MR. HILLBACK: And that's the fundamental point of process control versus batch control.

DR. LEWIS: Feedback loops.

MR. HILLBACK: Yes, whatever. Managing the flow as it keeps flowing, instead of trying to stop it all the time and see how it looks.

DR. LLOYD-PURYEAR: So then that really is also imagining a whole provider community that's actively involved in supplying this clinical --

MR. HILLBACK: This is actually what happens now, Michele.

DR. LLOYD-PURYEAR: Not in an organized fashion.

MR. HILLBACK: Not in an organized way, that's right.

DR. LLOYD-PURYEAR: But you have to create something that's actually organized --

DR. McCABE: That's our goal.

DR. LLOYD-PURYEAR: -- where people are weighing into this.

MR. HILLBACK: Our goal is to make it more organized, but it happens today. That's what our lab directors sit there and try to do every day.

DR. LLOYD-PURYEAR: It happens passively today.

DR. McCABE: Joann?

DR. BOUGHMAN: Hopefully, we actually reached a turning point today with the panel and some of the concepts that we moved into that the regulatory agencies now have come out on the table and said we want this information in structured ways, so that we can incorporate it, and remember that oversight is a larger term than regulate.

DR. McCABE: Yes, I think that's important, and I know that people have been discussing that over lunch and at breaks. We need to put that explicitly into the document that oversight is a much broader issue than regulation, and I think that that will also help build credibility with the public, who is much more concerned about some of those other aspects of oversight than they are about the pure regulation.

Yes, Dr. Feigal?

DR. FEIGAL: The one disconnect I have is sort of the twin theme that these things are home

brew because any given test is available for so few patients, and then the notion that we'll be learning things so rapidly that we won't be able to keep up with describing what we know. If there is really that little data that we can't even commercialize these tests, I think we shouldn't get our hopes up that after a period of time we'll have learned a great deal more.

MR. HILLBACK: I would certainly like to think that we've commercialized tests when they're home brew. Kit doesn't make it commercial. Kit only makes it something that one company decides to make --

DR. FEIGAL: No, I realize that. There can be a central lab that supplies a whole country, but part of what we've been dealing with, though, is this paradigm that for many genetic conditions, we will be dealing with very, very small data sets, and so I think --

MR. HILLBACK: But one of the other reasons why I think people don't want to make a kit is our situation with nine different versions of a CF test in nine years. So if we are in that mode that we have to make a new kit every year with a directions insert, and a new et cetera, et cetera, it's crazy to do. We're doing 15,000 or something CF tests a year now.

DR. FEIGAL: See, the purchaser of a test doesn't think it's crazy to have a new package insert that describes the current use of the information and the product. So I think what the question is is sort of what should go through the different regulatory hoops. I don't think that you meant to say that you wouldn't share with your users the most current information about --

MR. HILLBACK: No, absolutely not. We do prepare the data, but it's the process of going through a set piece regulatory process every year and making up vials with something different in it. A production process validation to make solutions to sell to other people is somewhat more complex than making it to use for ourselves.

DR. FEIGAL: I think the other disconnect that we need to think about is that in some respects, as you pointed out earlier, Elliott, this is much higher standard that's being set for many tests.

On the other hand, the standard of reproducibility and the oversight that occurs as different labs try and use the same thing is going to be completely absent from some of these, and we won't have a clue whether some of these labs are competent or not.

MR. HILLBACK: When you say reproducibility, you mean from day to day?

DR. FEIGAL: Can be used in more than one laboratory.

MR. HILLBACK: That's right. In fact, the issue is that each laboratory designs a test in its own way and it has to be consistent onto itself, but not necessarily consistent in the sense of reagent design as someone else. But if I say that we're testing for delta F508 and R117H, et cetera, that's what we're testing for.

DR. FEIGAL: I'm just pointing out, I think that we'll find there will be laboratories that will not have standards that would meet any kind of regulatory approval or any kind of CAP standard, either, and they'll cruise underneath the telephone wire because of the vast number of these kinds of tests. There really isn't a good framework.

MR. HILLBACK: I don't think that's true. I think the whole CLIA discussion -- there's been a long discussion at the task force about the research laboratories and some of the problems that research

labs are going to go out of business because they couldn't meet CLIA, and we had a couple of members from the genetics community who ran research labs, but as that discussion -- and Steve Gutman was there for a big part of it -- it became very clear that it is not that onerous to do what's right in terms of qualifying and putting in the procedures that assure reproducibility of test results, and if you're testing for this mutation that you can find that mutation reproducibly. That's not that hard to do. It's a minimum standard, but it isn't that hard to do.

DR. McCABE: I want to move on to the fourth question, then, and I've reframed it already, analogous to what we did with the third one, and that is to say, "What additional or different oversight options are needed to address genetic tests that have significant social implications?" Because as I've heard the discussion, it's not "Are there additional," it's really "What are these additional?" Is that a fair rewording of that?

Wylie?

DR. BURKE: I think that's a fair wording, and I think we should leave it that way. It may well be, as we define different oversight categories, that just automatically, when there's social implications, that's one of the reasons it falls into a sort of higher oversight category.

DR. McCABE: Right.

DR. BURKE: But I think it's such an important issue for discussion that we should keep it as a separate point.

DR. McCABE: But I think, from all I've heard the last day and a half, that there's no question but that there are additional. It's just what are they and how do we accommodate this?

Muin, did you have a comment?

DR. KHOURY: No, I was going to ask what "significant social implications" mean?

DR. McCABE: Yes. I think that that's one of the things we'll need to address, and that will get back to the categorization.

Wylie?

DR. BURKE: The one thing that we explicitly discuss in the document now is the possibility that there might be particular issues when you're targeting a test to a particular minority population, but actually, in terms of the conversation that's gone on the last couple of days, I actually think any test that is being proposed for universal screening might fall into that category.

DR. McCABE: Pat Barr?

MS. BARR: I just wonder if we need one more question, and I think it's in these four, but I think the community would like to hear, which is what special provisions will be made to see that orphan disease testing, once done, once considered useful, will continue, because now when it's done by one researcher, if that researcher retires, there are problems for that community. So somehow specifying that we're thinking about the orphan diseases as different might be helpful to people who will be looking at our document.

DR. McCABE: Well, it's broader than that. Could we make it "What special provisions will be made for orphan diseases?" And it will include, then, the issue of retirement, but there are other issues that we were hearing some discussion of before.

DR. BURKE: I wonder if that's included in "significant social implications."

MS. BARR: I think it is, but I think there's a community that's going to be looking at this document that does orphan disease work and relies on it, and I think we need just to be clear that we are aware of that.

DR. BURKE: And I guess my question is can we address that by adding orphan diseases to the last point?

MS. BARR: Oh, okay.

DR. PENCHASZADEH: I wonder if the significant social implications should have like a list of --

DR. BURKE: Including tests for specific populations, tests used for universal screening, and tests for orphan diseases.

PARTICIPANT: And behavioral genetics.

DR. PENCHASZADEH: Behavioral genetics, right.

DR. McCABE: Sarah has raised the issue that as we've reframed these questions about how and what additional, do we feel that the public is going to be able to address those? I think certainly those that have specific disease interests -- Mary, maybe you could address this, but I would think the constituencies of your groups would be able to have ideas about how and what.

MS. DAVIDSON: I've done a kind of beta test because I've sent this out by e-mail, as well as by our monthly newsletter, a couple of different times, and I've been very surprised at how little response I've gotten in terms of a real content response. People are very interested in the issues, but as they're framed in these questions, I don't think we'll get as broad a public input as we'd like.

As I've been sitting here, and I've been trying to catch Judy's eye, I've been thinking about the January 27th meeting and bringing the public together, and whether these are the questions that we will use for that meeting and whether there would be really kind of further elaboration in the questions.

I don't have an immediate answer to it, but it is a concern that I have, and that's why I liked in this last question breaking it down, so it doesn't just say "significant social implications."

DR. McCABE: These aren't necessarily -- I think, as we were talking about before, the questions that we're going to frame with the four questions are really a bit different. These are really I think more for us, almost, and to make sure we're dealing with these and that we address these in our final report.

MR. HILLBACK: I thought we talked about the concept of questions that really focuses on the individual. You know, questions that ask how would you feel if this impacted you or could impact you in this way or that way? Back to Judy's comments, and Pat's and other's, that we think about them as patient-oriented, or individual -- I shouldn't always say patient -- individual-oriented questions. So they will be answered by broad different groups of the public, but (inaudible).

DR. McCABE: Okay. It's time for us to take a 15-minute break, and we will come back at 3:15 to discuss really going back over this document in terms of some additional specific issues. We'll try and

wrap up the two-day session.

(Recess.)

DR. McCABE: Let's resume, everybody. What we need to do now is go through, and I think we've had some consensus on this, but we need to review the consensus, basically, and perhaps if we feel that we've already had these discussions, we could even finish a little early or discuss some other issues.

We're now at 3:15, and we're at the discussion/approval of draft consultation document and outreach mechanisms, and I think we discussed before the break how we will proceed, that basically we will make the changes in the consultation document that we have discussed here, we will bring those to the committee at our November 9th conference call, but we will be cautious not to embellish, so that it's really the discussion that we've had publicly.

We will have in essence three documents. We will have the executive summary, we will have the full consultation document, and we will have another document that will be framed somewhat along the questions. It will be basically the question parts of the consultation document, beginning around page 25. It will be the major questions, some subquestions and issues that we want the public to address, but then we will have an open-ended part at the end to make sure that if there are other opinions, concerns from the public that they would like to address, that we don't shut them off by not having that.

That's pretty much what I've heard. Is that acceptable to everyone around the table? Is there anybody who disagrees and would like something different than that?

MS. BOLDT: Are these conceptual questions going to be included, too? You said that they were more for our internal use, or is that to be framed for the public?

DR. McCABE: Why don't we have some discussion on that? I think the concern is that these questions will be accessible to a fairly limited segment of the public. I think that they are to some extent directing us to where we need to go with our final document, but I think that they should either be in the executive summary and/or in the questions document. I don't know what we're going to call that.

Yes?

DR. BOUGHMAN: It seems to me that the four questions as we have framed them here in fact could be a part of the executive summary document. After all, that's why or that's how we actually got started, so it is part and parcel.

However, I might suggest that in the questions document, with some introductory comments, and the science writer and staff can certainly toss this around a little bit, but even Question Number 1, if we really want to get feedback, rather than having the question as written, to merely say something like, and I'm literally scribbling here, "Defining the risks and benefits of genetic tests is a complex process. Is it possible to assign different tests to various oversight categories? What factors do you think are most important in determining the type of oversight needed and why?" The purpose of the test -- for example, diagnostic versus predicting a condition; the frequency of the gene in the population; having an intervention or treatment available; the severity of the outcome or condition in question; with what degree of certainty the test predicts an outcome.

And simple things like rephrasing the question, "What factors do you think are most important," rather than saying, "What factors are most important" or "What factors are important?" That implies that there's a correct answer, and what we want to know is what they think.

DR. LEWIS: Yes.

DR. McCABE: Yes, Pat?

DR. CHARACHE: Question 2, "Are the distinctions between clinical validity and utility important," I'd be sure that the definitions were there if that question's asked, as distinct from part of the summaries in which the definitions are provided.

DR. McCABE: So getting back to the original discussion, do you want these that we've -- and we've got to be careful that we don't confuse which Question 1 we're talking about, but the questions that we were discussing, these general conceptual questions, do we want those for the public?

I take it from your comments, Joann, you were indicating that you thought they could be framed in such a way --

DR. BOUGHMAN: Well, this document was still on the top of my notebook here, so I just translated it for example's sake. Whether we go back to the issues and reframe them in this type of language, however --

DR. McCABE: Yes, that's what I think.

DR. BOUGHMAN: -- I think the concept from my point of view is, unless we ask more specific questions, we're not going to get information that is digestible in any format. If we give enough questions and in the introductory comments say, "Address whichever of these you would care to," so that people know that they don't have to sit down and spend hours -- there may be one issue on their mind, and it may be the frequency question and it doesn't matter that it's a rare condition, it's important that it stay on the agenda, that still is a message that we need to hear. So I'm not wedded to any specific set of questions.

DR. McCABE: So it was more of the framework that you were suggesting.

DR. BOUGHMAN: The concept.

MR. HILLBACK: I think we need to remember that there are lots of publics, and there is a sophisticated public, which includes members of the American Society of Human Genetics or of the Washington lobbying public or other companies that are not represented here, et cetera, as well as my mom or my cousin or whoever. I think we need to make sure that we create an array of questions that may get an array of answers, depending on what different parts of that public want to focus their attention on.

So I do think we should keep the more philosophical questions somewhere in the list, as well as the more pointed, you as an individual, how would you want to deal with it? I think we want both, don't we?

DR. PENCHASZADEH: Are we talking about the public consultation by mail or are we talking about the meeting in January?

DR. McCABE: Both, both.

DR. PENCHASZADEH: I think they are two different levels. At least in mind, I was thinking the mail-targeted consultation will be probably addressed directly to more learned types of people.

DR. McCABE: Well, if you look at the list, it's really a broad variety of people.

What I see, we will have available on the Web site the long document. What will go out in the public consultation, is that going to include the long document? My understanding was, what was planned to go out in the consultation was the long document, the executive summary, and I think these issues that we talked about before the break fit more into the executive summary and sort of where we're going as we begin to frame the details, and then the third document we talked about this afternoon, which was the questions and trying to frame a series of questions and subquestions under the four issues.

So I think that they could all go, but I see that these issues would go into the executive summary and into the main document. I would like to send everything out, though, because I think it would be important to have feedback on the entire packet, if that's acceptable, and that was budgeted in, right, in terms of the weight of the mailing?

Joann?

DR. BOUGHMAN: That may be the best answer. I'm just challenging myself with the idea that the executive summary should be so good as to stand by itself and the cover letter merely have the Web site listed with the longer document available, rather than sending out the long document, but I'm just trying to remember the 76 pages of names and addresses.

DR. McCABE: Yes, the concern about that is that there are some members of my faculty who don't understand e-mail, let alone the Internet, and so as we talk about getting out to a broad variety of individuals, I would hate to have somebody not respond because they were not facile with the computer.

DR. BOUGHMAN: Well, that's true, except that when you have a 50-page document, I'm going to bet people aren't going to xerox the 50-page document anyway to in fact distribute it to any individuals, whereas if we send out only the few-page summary and the questions, they might xerox that package.

MR. HILLBACK: Well, the thing will be available on the Web.

DR. McCABE: Yes, we can make sure in the cover letter that the URL is there, and then we've got it both ways, if that's acceptable.

Does anybody object to sending out the long document? Yes?

DR. LEWIS: It's another issue, but one of the things that I believe, and I'm sure our science writer will deal with, but just to make sure that we're looking at level of readability of the documents that are going out, especially for the ones for the broad public consultation and the ones that go on our Web site, to make sure that the level of readability is at whatever patient education material is supposed to be at, so that we have something that's understandable.

You're shaking your head no?

MS. BARR: I actually think it's going to be too difficult to do that for the large document.

DR. LEWIS: No, I'm saying for the short document.

MS. BARR: For the short document, yes.

DR. McCABE: At one time in my life, I actually was involved in developing patient materials, and I remember the formula. It has to do with the number of syllables per word, the number of words per sentence, and the number of sentences per paragraph, and from that you end up with your grade level. The nature of our words is that I think it's going to be hard to get it below a college level. Maybe it's possible, but some of the words are pretty long and pretty sophisticated. We can try. Right now, it's written at a college level.

Is it possible? Did you even look at that, about getting it down? Sarah is saying that they tried to get it below a college level, and it was just difficult.

MS. BARR: Do you think you can get the public questions below college level?

DR. McCABE: Yes, that I think we can do. That we can work on, and I think the questions there we can be very sensitive. Again, that'll have to do with doing it in more bullet form with the questions, which basically does away with paragraphs and lets people focus on individual questions, and we can work to make sure that they're short and very straightforward.

DR. LEWIS: That was the piece I was getting to, is the piece that goes out for the general public.
DR. McCABE: That I think is doable.

DR. KOENIG: Now, is there a reason -- I mean, can we have different versions of the questions, though? I guess that has been raised, and I still endorse that.

I was just thinking about this in terms of the kind of process I go through as a researcher to find things out from people, and you have your own research questions, which is what you want to find out, but you never go out and ask people those questions. You then reframe those into an interview guide or a set of questions targeted to the population you're asking the question from. I mean, I never ask people my research questions.

DR. McCABE: Well, I think that was what Joann was walking us through, was to take it and make it more that way.

DR. KOENIG: But then I thought the conversation was going away from that, saying --

DR. McCABE: No, no.

DR. KOENIG: No, it wasn't? Okay. Then I misunderstood.

DR. McCABE: No, we would do that. It's just that was an example, and we will go back to the transcript to get the example, and then from that use that to craft the questions on the other prior issues, our four issues.

Ann?

MS. BOLDT: Just a real practical issue. In terms of the cover letter, I just want to make sure people realize that you don't have to read the long document to be able to answer the questions, because I think there are going to be a lot of educated people out there returning that, too.

DR. McCABE: Okay. The other things that we needed to deal with, then, we had talked yesterday about a Steering Committee to help plan the January 27th outreach meeting. Given the size and number of breakout rooms that we were talking about, my guess is that we're going to be drawing on a

number of you. The Steering Committee, though, I think should be Judy and the people who are in the Baltimore/Washington area. Definitely, Joann, since we're going to be at the Baltimore Campus of the University of Maryland.

My guess is we're going to call on many of you to be a part of that. There will be a small Steering Committee, and then a larger group, and if anybody wishes to volunteer or has a particular interest in that, I'd be happy to take volunteers, but those of you who don't volunteer may be volunteered anyway.

Anybody wish to volunteer?

DR. PENCHASZADEH: (Inaudible.)

DR. McCABE: Yes.

DR. PENCHASZADEH: So I don't need to volunteer myself, but I --

DR. McCABE: Okay. So Victor's going to volunteer voluntarily.

(Laughter.)

DR. McCABE: And Reed. Good. And Ann, also.

DR. BOUGHMAN: One of the things that Dr. Alpert said last night, too, was that in fact there is some agency or others who have facilitators or there is a contract or something to do with meetings, and it could be that we might be able to handle some of that, given the reduced cost for facilities or something like that. So that it could be that some of the members in the Steering Committee could be paired with a trained facilitator for the afternoon session, so that in fact might work things more smoothly.

DR. McCABE: Sarah says we'll work on trying to do that.

DR. LEWIS: Ed?

DR. McCABE: Yes?

DR. LEWIS: Can I also suggest that those people we did some outreach to in terms of consultation, that we involve some of them, too, because I think that would be important.

DR. McCABE: Yes, and definitely Vence Bonham. We should try and involve both Vence and his constituency, the people he's been working with.

DR. LEWIS: And the people we spoke with on the phone.

DR. McCABE: Yes.

DR. PENCHASZADEH: I would suggest also the group involved in the genetic dialogue that were actually from the Baltimore/Washington area.

DR. McCABE: I'm sorry?

DR. PENCHASZADEH: For the public consultation, the group from Howard University here.

DR. KOENIG: Ilana Mittman.

DR. PENCHASZADEH: Ilana Mittman, that's right. They were involved in the Baltimore/Washington area doing community groups. She might be a good person.

DR. LEWIS: Those were the people I was referring to that we spoke with on the phone.

DR. McCABE: Also, any other suggestions you could give us on experts to serve on that, that would be good.

There's the summary document that was sent around last week. I think we've talked about that. I don't know that we need to go through that and wordsmith that. Do we need to go through the summary document, the executive summary? Is there any need to go through that?

MS. CARR: No.

DR. McCABE: Okay, and then other issues. We talked a bit about education and some issues about education of professionals and the individuals of the community more broadly. Do you have any thoughts on that?

Yes, Pat?

DR. CHARACHE: I don't think any regulatory or other oversight will be successful unless those who are ordering the test have a better level of understanding than they have now, because otherwise you're just using a regulatory wall, and the goal of the uninformed user will be how do I get under it or over it, as opposed to helping.

DR. LEWIS: Ed?

DR. McCABE: Yes?

DR. LEWIS: That may be something that as we wind this issue down, that may be something that we want to think about taking on as our next priority, is looking at some of those education issues.

I was out at ISONG this week, which is the International Society of Nursing and Genetics. There were several reports there about ELSI-funded projects that were dealing with educating large numbers of nursing faculty to include genetics in the curriculum, so we may want to look at that and other kinds of programs in subsequent meetings and have those kinds of presentations.

DR. McCABE: I think that will extend beyond the March 15th.
DR. LEWIS: Yes.

DR. McCABE: But certainly education is going to be very important for the implementation of any of this, so that can be high on our list.

Yes, Pat?

DR. CHARACHE: I would hope that the need for this will be included in the executive summary.

DR. McCABE: So we can include something on the need for education. I had that in my notes

from the last two days.

DR. LLOYD-PURYEAR: And that's both public and provider education.

DR. McCABE: Right, right, yes.

DR. KOENIG: But hadn't we had, at least on the table, the issue of linking the two? I know that this is a model that people don't like, but it's been used in the past for other things, you know, actually requiring certain education to order particular tests, or is that something that's just so horrible to consider that we don't even want to raise it in terms of linking education and oversight?

MR. HILLBACK: We tried that.

DR. KOENIG: You tried that? Oh, you tried it in -- so the task force has been there, done that, so we aren't going to talk about it?

MR. HILLBACK: I didn't say we shouldn't try it. All I said was we tried that. It went down in flames.

DR. KOENIG: I don't know if it's a good idea. I'm just surprised it hasn't even come up, that's all.

PARTICIPANT: Let's try it again.

DR. KOENIG: No, I'm not endorsing it.

DR. McCABE: Do we need to do that before March 15th? I think it would be hard to do that before March 15th.

DR. LLOYD-PURYEAR: Again, there is sort of a model within the pediatric vaccine world. Every time you give a vaccine, you have to hand out a vaccine information sheet, where you go over the risks and benefits and potential adverse reactions of the vaccine, and then get that signed off on. So that was in a law.

DR. McCABE: But I think what Barbara is saying is the education of the person doing the vaccination.

DR. LLOYD-PURYEAR: Well, but that process of informed consent requires the provider to be educated.

DR. KOENIG: No, actually, I was talking about something else. I think it happened at the beginning of the HIV epidemic, when there were certain instances where we actually mandated that people had to demonstrate a continuing education course in HIV before they actually were able to order the tests.

DR. LLOYD-PURYEAR: That's states, though.

DR. KOENIG: And some certain states instituted that kind of regulation.

DR. BURKE: If I could comment on that, the State of Washington was one of the states, and rapidly there was produced by the state medical association a four-hour CME that you could do at home to meet that requirement. It was pro forma. I think it probably did some good. We also have a mandated

pre-test counseling process and a checklist to prove that we've done pre-test counseling.

So such things can be done, but quite honestly, I don't think, in the way they get implemented to meet a mandate, they provide the kind of depth that we're really interested in, and I think we really open ourselves up to a major problem with genetic exceptionalism, because all clinicians are I would say flooded with new information and new technology all the time. It's part of practicing medicine. I think we need to be very cautious to carve out a special CME requirement in genetics. I think that'd be a tough issue.

DR. McCABE: And it could have implications for access, too. I mean, if you really set the bar high, that could have significant implications for access.

DR. BURKE: I think we should continue to talk about creative ways to ensure that education occurs. My comment is really just that what seems simple and firm, like a CME requirement, I think would be very problematic.

DR. McCABE: One of the things that I want to do before I forget, and Sarah has reminded me, is that I really need formal approval for the five outreach mechanisms that we discussed. So are people comfortable with those?

DR. LEWIS: Would you like me to move that?

DR. McCABE: Okay.

DR. LEWIS: I can move those on behalf of the subcommittee that was presenting the report, if that's helpful.

DR. McCABE: Thank you, Judy.

Do I have a second?

DR. PENCHASZADEH: Second.

DR. McCABE: Any further discussion on these outreach mechanisms?

DR. KOENIG: With the changes that we talked about during the meeting.

DR. McCABE: Yes.

DR. KOENIG: To be incorporated.

DR. McCABE: Okay. Do you want to --

DR. KOENIG: With those specific changes about --

DR. McCABE: Can you speak into the microphone, please?

DR. KOENIG: Sorry.

There were some specific changes, for example, under how we were going to do the outreach that were recommended by Vence Bonham and his group, those kinds of changes.

DR. McCABE: But the overall outline was the same five categories that we had discussed.

DR. KOENIG: Yes.

DR. McCABE: Any further discussion?

(No response.)

DR. McCABE: All in favor, say aye.

(Chorus of ayes.)

DR. McCABE: Any opposed or abstain?

(No response.)

DR. McCABE: Okay. It's unanimous.

Also, some of you have been sitting in the audience throughout parts of the last two days or all of the last two days. Any comments that any of you might have? Any further input that you would like to make at this time for us as we move on to the next step?

Yes, please? Please identify yourself for the transcript.

DR. FRANK: Tom Frank from Myriad Genetics.

One quick comment about the mechanism that Dr. Khoury described. It's an excellent mechanism, but I do want to remind everybody that those were tests for which most of the data came from clinical testing, and I think the challenge is to avoid a chicken and egg paradox where, to introduce the test, you need the clinical data that you don't get until you introduce the test. I'm not saying that you can solve that problem in the next two minutes, but that's something that I didn't hear a solution for.

DR. McCABE: Yes, Muin and I actually talked about that as he was heading toward the airport, and I think what he sees those as are models from which we can learn, so that we can then -- we can't afford to do that for every disease. I think your point's well taken that we can't have the oversight begin to govern access, and we've discussed that before, but I appreciate your highlighting that for us.

Wylie?

DR. BURKE: Yes, and I think just as a follow-up to that, it might well be that the most important thing that comes out of that process is an agreement about what kind of data we're going to need over time and ongoing evaluation of tests, which is both a commitment to ongoing evaluation and some guidance as tests come into use about what kind of data needs to be collected, so that at least over time we can answer questions we consider crucial, even if we all recognize we can't answer most of them when the test is first available.

DR. McCABE: Yes, please?

DR. BUCHANAN: Allen Buchanan, the University of Arizona.

I think the topic of genetic exceptionalism has come up a number of times in my presentation

yesterday, in discussion yesterday, and in remarks by Dr. Burke just a few minutes ago, and I would just make a plea that somewhere very early on in your document that you face that question head on. It just won't do to say the reason we're talking about genetic tests and not other tests is because this is the Committee on Genetic Testing. I know you wouldn't do that, but I just think that you open yourself up to criticism, and I think you do have a good answer beyond just saying that's the name of the committee, but I would urge you to go ahead and just be very upfront about that and confront that potential objection that you're being arbitrary and, in a way, discriminatory in imposing a special burden on genetic testing without good reason.

DR. McCABE: Thank you.

Yes, Pat?

MS. BARR: I know you said that at some point we would look at the licensing and patenting questions, because we saw that as part of the larger modality of oversight. Do you have a sense of when we would do that and was it decided we would do it after -- I guess we'll have to do it after March 15th.

DR. McCABE: Yes, I think that we will have to do that after March 15th. So I hear that education is an issue that we need to address, the patenting is an issue, and there's one other issue I want to take up before we're done, but Jim, you want to identify yourself, please?

DR. HANSON: Yes, Jim Hanson, National Cancer Institute.

It's sort of two related thoughts. One is that it occurs to me that, although I wasn't here for all the discussion about the outreach activities, one of the Department's activities that is addressed to the public health community is the Healthy People 2010 document, and I wonder if there are not elements of the efforts of this advisory committee that would not be appropriate for somehow or other integration into that. If there is a need to educate the medical community and the public health community, if there is a need to raise the level of understanding as to how to use genetic tests and when to use them, I wonder if those shouldn't be reflected in national public health planning in that agenda in some fashion, and perhaps it's worthwhile to know whether that is in fact happening.

By the same token, I would just like to register the notion that I think the way the committee is charged at the present time constrains it from carrying forward some of its expressed areas of interest and mission, and perhaps sometime at the conclusion of the committee's activities it might be worthwhile to convey that notion to the Secretary for her reflection for ongoing later activities.

DR. McCABE: Do you want to give us specifics, Jim?

DR. HANSON: For that? Well, I mean, it seems to me that when you say that the focus of the committee is genetic testing, what we heard over the last two days and at the previous meeting was that the test and its regulation may not be the central issue. That's an important issue, but the education of the health care community and the public as to how and when to use this, and the question as to what public policies might be controlling, are important issues. They're not exactly genetic testing, but they will set the framework.

So down the line it may be appropriate to rethink this committee as a committee on genetics or a committee on genetics and public policy or something of that nature, which would allow, then, for some of these other issues to be brought together in a coherent set of policy documents.

DR. McCABE: Thank you.

Along those lines, one of the areas that we had planned to discuss at this meeting, but were unable to because of Mr. Jennings having other obligations, was the issue of genetic discrimination. I would assume that we would like to take that up in the future, and see if we can continue to keep that on our agenda and try and work out an opportunity to do that. Again, it may not be possible before March 15th, but we need to try.

I see heads shaking. Do people agree that we should take that up in the future?

DR. CHARACHE: So moved.

MR. HILLBACK: I think it's absolutely crucial because it's part of what causes a lot of the other concerns about a lot of the other things we're trying to do. To not discuss it would be to leave out a major part of some of the issues.

DR. KOENIG: I think it needs to be addressed in terms of how it relates to oversight, and it's hard now for us to do that. I mean, I don't have at the top of my head all of the current efforts at privacy. There's some information that we don't have. You know, Shalala has another working group dealing -- I mean, aren't they going to be required to have regulations out about privacy in general within the next few months? So it's going to be hard for us to know what to recommend without knowing what is coming out of that other group.

DR. McCABE: Dr. Raub, would you be willing to comment? Could you come to the microphone, please? Are you willing to talk to us about that?

DR. RAUB: I'm Bill Raub. I'm Deputy Assistant Secretary for Science Policy at HHS.

I really can't elaborate more on what you just said. There is a major effort. Some of my colleagues down the hall from me have been going without sleep for the last two months in terms of meeting what is now the statutory obligation of the Secretary to propose a regulation. So that will be emerging soon and I think it will be something -- it will be out for public comment, of course, and will be I think of potential interest and obvious relevance to this committee's agenda.

DR. McCABE: Could you pass the word on to your colleagues, or I don't know if we need to do it more formally, but once that document goes out for public comment, this committee would like to have it come to us for our comment.

DR. RAUB: I'll be glad to pass that on for you.

DR. KOENIG: And one of the reasons that's particularly relevant is because it helps to combat this charge of genetic exceptionalism, because then we really are then trying to place the whole issue of genetic privacy within the larger issue of confidentiality of medical records and their use in the criminal justice system and across a whole broad array of bureaucracies.

DR. RAUB: I'll be glad to do that.

DR. McCABE: Thank you very much.

The other thing that I wanted to mention that we had put on the agenda for February, because we had discussed it back in June when we first met, is that HRSA, Michele's group, and the American Academy of Pediatrics co-sponsored a task force on newborn screening. That report will be out very shortly. It's in penultimate draft right now, and we were planning to have that task force report presented

here, because it takes up a number of issues that we've discussed as a program with close to 40 years' experience and the issues that are still outstanding, as well as those that have been solved over that period of time.

Is that acceptable to everyone, that we'll put that on the agenda? Yes, Ann?

MS. BOLDT: Just another quick comment. I was thinking about what Barbara brought up in terms of ensuring the competency of individuals that are ordering these tests, and I know that I had asked this on a conference call and Elliott had included that in some of these documents, but I'm not finding it now, so I'm just wanting to make sure it's still in here and if you could direct me to where that is, and that there is a different level of oversight in terms of assuring that health professionals are competent in terms of ordering testing, but that we couldn't focus on that at this point, but in some ways do we want to frame any questions to ask that of the public?

DR. McCABE: It's on page 5. Let me tell you, Sarah found it. She has it memorized. It's on page 5, like the second full paragraph.

MR. HILLBACK: Thank you, Sarah.

DR. McCABE: And it's also in Issue 3. "But it is important to note that although this paper focuses on federal oversight of genetic tests, the training and education of health care providers is another critical issue," and it talks about the need for additional education. It does not say it quite as explicitly as you did, Ann, but more talks about the need for training.

Also, on page 32 --

MS. BEARDSLEY: The paragraph right before the subhead, right before the paragraph, that talks about options.

DR. McCABE: So the paragraph that starts "Before outlining the options," it says, "Training and education of primary care providers who prescribe genetic tests and use the results for clinical decisionmaking is a critical issue," and goes on to talk about it there.

MS. BOLDT: I can't remember. Is that in the short document, too?

DR. McCABE: We will note your comment and make sure that education is in the executive summary.

DR. TUCKSON: Are we suggesting going beyond these kinds of issues, of the way they're stated now?

DR. McCABE: No, all I was hearing was that it needed to be highlighted and to be sure it was in the executive summary.

MS. BOLDT: But if we're going to pose a few more questions for the public, do we want to frame another question in terms of oversight in that area? I don't know. This is a great opportunity to do that.

DR. McCABE: I think we can build it into the four issues that we have and talk about their need for education under those four issues, but we can make sure that it's in there.

DR. TUCKSON: I think if we're going to do it, we're going to need then to make sure we have some -- you know, the context of this, how in fact professionals are -- you know, in terms of how their competence is determined, this is a very big issue. I just want to make sure we don't really set up something and we start going down a road that we haven't thought about fully yet.

DR. McCABE: My interpretation of it was that we were going to take what is in the document, which really doesn't set a level of competency or a need for certification of competency. It more says that this is an issue, and then we could pursue it after the 15th.

Yes, Wylie?

DR. BURKE: It's always good, obviously, to be sure that we get as open-ended public comment as we can. On the other hand, I'm not sure it's going to be useful to ask for public comment upon whether docs should have education in order to be competent to use tests. In other words, it's almost a question that leads to only one answer. You know, yes, of course they should, and if they're not competent now, they should be made competent.

To me, this is much more of a difficult issue of determining what is required to be competent to use genetic tests. It's more of an empiric question.

DR. McCABE: We will look at that as we draft the document for questions.

Yes, Pat?

DR. CHARACHE: I think this is a very complex issue because right now competency is in the eye of the beholder, and everybody thinks they're competent because they lack the database that shows whether or not they are.

DR. PENCHASZADEH: It seems that all the issues that we tackle are complex.

(Laughter.)

DR. PENCHASZADEH: And I want to add another one, which to me seems a kind of background to everything, which is access to health care, and specifically to genetic testing. My personal belief is that we should tackle that issue at some point. There are 43 million people in this country who have no health insurance, and it wouldn't make good service to the population in analyzing a lot of things about oversight, about education, about everything, if we don't make some strong statement about access to health care in general. I subscribe to the notion that we shouldn't rely on genetic exceptionalism, particularly with genetic testing and in terms of access, but I think the issue of access to health care and testing should be something that we tackle.

DR. McCABE: I think it's in here in terms of access to genetic testing. I remember reading it. I think in terms of access to health care overall, that's probably more than we can do between now and March 15th.

DR. BOUGHMAN: I believe that to be true as well, but being a replacement for someone on the Task Force to Conquer Cancer in the State of Maryland right now that is addressing some of the tobacco settlement issues, it was framed in a way that I think that we may be able to weave it in very nicely here. In cancer and in the terrible rate or frequency of new cancer that we have in the State of Maryland, in spite of the fact that we have NIH with NCI and all of that, Hopkins and the University of Maryland, having one of the highest frequencies, this has come up over and over again about access to early

detection, but in fact it was tied to why detect it if you're not going to have the wherewithal to intervene.

I think that those two end up getting tied together here vis a vis the newborn screening route and/or some of these others, and therefore is tied to the testing issue. I think that's one of the differences in labeling, stigmatizing, a newborn with PKU versus an older individual with another kind of disorder, not only that there is an intervention or a treatment, but in fact access to that is guaranteed.

DR. LLOYD-PURYEAR: In some states.
DR. BOUGHMAN: True.

DR. McCABE: Right, and that's one of the issues that the Newborn Screening Task Force takes up, because despite the fact that from the very beginning newborn screening has been tied to intervention, as Michele points out, it's not --

DR. BOUGHMAN: It's not universal.

DR. McCABE: It's not universal in the United States at this time.

Are there any other issues that we need to address?

DR. TUCKSON: Not to prolong this, but I just want to make sure I lock in what we just did. The comment about access was important, and what I think we've just heard is that there are many people who view the question of access to the diagnostic test as being irrelevant if you don't have access to any intervention.

So we thought maybe the question of access to care was not within the bounds of our scope, but if we're having to deal with people in the world who say, well, why have access to the testing if you don't have access to any intervention because you don't have any insurance, I just want to make sure that that didn't go by me too fast here.

DR. BOUGHMAN: Well, it's probably my being so tired and I didn't make it clear. In fact, I think that the two questions, the testing and the ultimate access to care, are inextricably entwined.

DR. TUCKSON: That's right.

DR. BOUGHMAN: And I think that while we are a committee that has been charged with issues on genetic testing, I believe we do have the opportunity, once again, to at least state that in fact it raises additional questions and issues.

DR. TUCKSON: That's helpful, because I've been struggling for the last two days with this notion of the individual being able to go and purchase whatever they want. They can purchase the testing they want and make the decisions they want, so even no matter what we recommend overall, I mean, this is not a totalitarian society, so this really does become in many ways a prototype for the two-tiered, three-tiered health system in this country.

I think that these are some issues I certainly want to know more about as a context for our recommendations and work, because it could be very easy that people could say, you know, well, to heck with you. You don't have any insurance anyway, so why are we worrying about your access to the diagnosis?

DR. McCABE: We heard, though, an anecdote from one of our presenters, however, that

individuals may want to order the test without going through a physician and without formal medical follow-up because of the concern about discrimination. So I think those get tied in as well, and there may be people who elect not to have it tied to care because of concern that the tie to care then develops a medical record, which they don't want necessarily to have.

Pat, and then Wylie.

MS. BARR: I think what you just said is quite different, in that I don't think that those people would necessarily choose to be tested if they didn't have access to care after the test. They don't want the test in the record necessarily, but I'm sure if they know that there's an intervention, they want the intervention.

DR. McCABE: Sure, sure. No, I agree. I agree.

Wylie?

DR. BURKE: And I just want to comment that I think all the issues that we were just discussing about access are implicit in a rigorous approach to clinical utility. That is, clinical utility it seems to me incorporates access to treatment, the nature of the treatment, whether it's safe, what kind of risks it poses, and to what degree it has proven efficacy.

I think all of those are part of determining whether or not there's a clinical utility, so if there's an effective treatment that is just plain too expensive or available only in a small number of places, so that it simply isn't functionally available to people, that's part of the measure of clinical utility.

DR. PENCHASZADEH: I'd be very surprised if one of the major concerns of the communities in the public consultation is not access to care after a genetic test.

DR. McCABE: Other points for discussion?

(No response.)

DR. McCABE: Well, I want to thank the committee, the people in audience who helped to advise us, and especially Sarah and her staff for putting this meeting together.

DR. TUCKSON: Can we also thank the chairperson who served diligently and facilitated a wonderful conversation?

(Applause.)

DR. McCABE: Thank you. Have a safe trip home.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)