Seventh Meeting of:

THE SECRETARY'S ADVISORY COMMITTEE

ON GENETIC TESTING

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P R O C E E D I N G S (8:00 a.m.)

DR. MC CABE: Before we started this morning with our program, I want to make an important and eagerly awaited announcement. The report of the Committee, Enhancing Oversight of Genetic Tests, has been received by Secretary Shalala. This key step in our advisory process allows us to release the report to the public. Copies of the report are now being distributed. The report will be posted on the SACGT website.

So we are extremely excited about this. I don't know about the rest of you on the Committee, but I have had numerous inquiries about the report, and I am personally extremely pleased that it is coming out, and the Committee is to be congratulated on your efforts for this, as well as Sarah and her staff. So thank you very much. Copies are coming around for all of you.

Going on with our program as we have scheduled it today, one of the assignments we had identified for the access working group was to organize a session on reimbursement of genetic tests. I am going to turn to Dr. Judy Lewis, the access working group chair, to introduce our panel of presenters and to moderate the subsequent roundtable discussion. I want to commend Dr. Lewis and the members of her working group for putting together such an interesting and informative panel, and to thank each member of our panel for being here today to help inform the Committee and the public about this important area.

Dr. Lewis?

Session on Reimbursement Practices for Genetic Testing Services

DR. LEWIS: Thank you, Ed. At SACGT's recent meeting on August 4, the Committee identified its next set of priorities, including issues related to access to genetic tests. To begin its exploration of access issues, the Committee requested a presentation on the current reimbursement practices and policies for genetic test services.

This session aims to provide the Committee and the public with background on the current practices and policies for reimbursement of genetic testing services by various types of public and private health insurance, including for-profit and not-for-profit managed care, indemnity, preferred provider organizations, point-of-service, Medicare, and Medicaid.

The goal of this session is to enhance knowledge of reimbursement issues and provide a foundation for the Committee's exploration of reimbursement issues and access to genetic test services. We have invited five experts from the public and private health insurance industry to present their organization's perspective on reimbursement practices and policies regarding genetic test services.

Following the presentations, there will be a roundtable discussion with the presenters and Committee members, and public comment period to provide an opportunity to hear other perspectives about reimbursement issues.

Our first speaker this morning presenting on Medicare and Medicaid is Jacqueline Sheridan. Ms. Sheridan is the Acting Director of the Division of Items and Devices in the Coverage and Analysis Group within HCFA's Office of Clinical Standards and Quality. This division is responsible for the development of Medicare coverage policies for laboratory services, durable medical equipment, prosthetics, and drugs.

Ms. Sheridan also leads the government interdepartmental support team for the Clinical Diagnostic Laboratory Services Negotiated Rulemaking. She and her staff analyze the scientific evidence surrounding new technologies in order to make national determinations regarding Medicare coverage. They also work with individual contractors on a case-by-case basis in an effort to assist them in reaching appropriate determinations on specific cases.

Thank you, Ms. Sheridan, for coming this morning.

Before we begin the presentations, I'd like to remind the presenters to limit their presentations to 15 minutes, so that we have time for questions in between presentations.

MS. SHERIDAN: Good morning. Thank you for the opportunity to be here today to talk to you about the Medicare and Medicaid program. I work primarily with the Medicare program, and most of my remarks will be directed to that program. I do have a few remarks about the Medicaid program at the end, but that is primarily a state-run program and has a great deal of variability, so there is not a whole lot I can say from the national perspective on that.

The Medicare program is an eligibility program. It is an insurance program that only covers a discrete set of beneficiaries. The Medicare beneficiary population are persons who are age 65 and older, people who have a disability and have been on a disability entitlement program for at least 24 months, and persons with end-stage renal disease needing routine dialysis or kidney transplant. This covers approximately 40 million Americans.

The Medicare program issues national coverage decisions on a very small

number of the thousands of services that are available to beneficiaries. We have approximately 300 to 400 national coverage policies. The vast majority of the coverage determinations in the Medicare program are made by the local contractors who process our claims. These are primarily insurance companies that have contracts with the Medicare program.

The local determinations can be on a claim-by-claim basis, or the local contractor can develop a local policy which is announced in their local publications, so that everyone has advanced notification of what the policies would be.

Whether the decisions on coverage are made nationally or locally, they are guarded by the provisions of the Social Security Act. The Social Security Act includes the benefits that the Medicare program covers, but it also includes a set of services that are excluded from coverage.

With regard to the issue of genetic testing, there are two statutory exclusions that potentially could come into play more frequently than others. The first is the exclusion in the Medicare program that provides that Medicare may not pay for services unless they are reasonable and necessary for the diagnosis or treatment of illness or injury. The second one is a provision that excludes routine physical checkups. We have historically interpreted these two exclusions to prevent the Medicare coverage of primary screening tests, because they are generally tested and are either provided as part of a routine physical checkup or they may not be reasonable and necessary for the diagnosis of illness or injury.

Medicare has interpreted screening as the testing for disease or disease precursors, so their early detection and treatment can be provided for those who test

positive for the disease. Primary screening tests are performed primarily when there are no signs, symptoms, or personal history of the disease that is present in the Medicare beneficiary. Medicare does cover testing for people who have specific signs and symptoms when the disease is not known, something that physicians generally call rule-out conditions. But if a patient has a symptom, even if it is a fairly vague symptom such as fatigue, a number of tests could be provided to diagnose what was causing that particular symptom. But if a patient is an otherwise seemingly healthy individual who has no particular signs, then the issue of screening comes into play.

Regardless of whether the coverage determinations are made locally or nationally, Medicare generally makes evidence-based determinations. The level of evidence differs between local determinations and national determinations, and the appeals proceedings of those determinations are different, depending on whether they are local or they are national, which reflect the level of evidence that is taken into consideration.

Whether the decision is local or national, they have a system that allows for public participation in it. Whenever HCFA is considering a national decision, that decision is posted on the Internet, and the public has an opportunity to participate in that. The local decisions have a public notice period that they go through.

In either case, the first step is that there has to be a Medicare benefit that the service can fall into. In the case of genetic testing, there is a Medicare benefit for diagnostic services, so this generally is not an issue.

For the purposes of national decisions, we have not yet published a regulation that interprets the provision of reasonable and necessity in the law, or provides

direction about when we can consider what basis we will go through in considering what is reasonable and necessary.

So for the past number of years in the Medicare program, we have operated under an operational interpretation of that provision of the law. The operational procedures that we look to consider the statutory benefit that exists, whether FDA approval is required and has been obtained for the item or service, the clinical utility or the medical benefit that is involved with the service, the appropriateness of the service for a particular patient population, and we look at the fact that the benefits of the service are greater than the risks involved with it.

With the issue of FDA approval, Medicare does require that if FDA approval or clearance is required for an item or service, that approval must have been obtained prior to Medicare coverage. So if FDA would begin to regulate genetic tests other than the kits that it currently does regulate, Medicare coverage would be conditioned on that FDA approval.

I do want to point out that the Medicaid program does not nationally have a similar requirement with regard to FDA, so states have the ability to take into account FDA regulations as they deem appropriate.

In looking over some of the background information I had with regard to your Advisory Committee, I noticed that there is a difference in the way that we look at clinical utility. My impression is that for the most part, the Committee has considered clinical utility more an issue of clinical validity, where the Medicare program looks to the health care outcomes or the changes in management of the patients that are associated with a particular test. So it makes the issue of predictive testing, particularly in a

situation where there is no known treatment of a patient, difficult for the Medicare program difficult as far as coverage is concerned.

At this time, the Medicare program has not issued any national coverage policies related to genetic testing. All of those decisions that have been made with regard to genetic testing have been made at the contractors' level, using their individual guidelines of case-by-case or local policies. Medicare has made a substantial payment for certain diagnostic genetic tests that are not screening tests under this local contractor authority.

I wanted to talk a few minutes about what the local contractors use in making their decisions when they are developing a local policy in opposition to case-by-case. If a contractor decides that it wants to develop a local policy for a genetic test, it would need to take that issue to its contractor advisory committee. This is a committee that is composed of representatives of major medical organizations and other health industry representatives in that particular local jurisdiction of the contractor.

Each contractor has a physician who is a medical director, and a team of nurses who provide support to the committee in developing draft policies and taking the issues to the committee. Once the committee makes recommendations with regard to the local policy, the contractor will prepare a written detailed policy down to the code level. It talks about CPT codes and in particular ICD-9 codes so that the users of the policy will know exactly what the expectations are on a claims processing basis when they are submitting claims, on which kind of claims will be paid and which kind of claims will not be paid.

That is sent to a broad spectrum of the public for public comment. The

public comments are considered by the medical director and the carrier advisory committee when appropriate, but the committee is bound to consider but is not bound to necessarily change a particular policy in response to public comment. A number of public commenters will be represented proprietary interests, and so the committee will take those comments under consideration from an objective body, and develop a policy which then is published for at least 30 days prior to the time that it is implemented within the contractor's jurisdiction.

The contractors do share contractor policies in an effort to promote some consistency, but even if they are using a policy that has been adopted in one region, they need to take it to their individual advisory committee for their particular jurisdiction.

Some of the tests that the contractors have covered under their local jurisdictions include a lot of molecular diagnostics, interpretations, separations by gel electrophoresis, amplification in nucleic acids, mutation identification by sequencing, and enzymatic digestion. They also cover alpha fetal protein and a number of chromosome analyses.

The national coverage policy differs somewhat from the local policy. Everybody is entitled to submit a request for a national coverage policy. We published the procedures in the Federal Register and we post them on the Internet. The kind of information that needs to be submitted with the request can vary, depending upon the technology that we are considering. For some breakthrough technologies, we would expect a different level of scientific evidence than for a technology that has been around for a long time and has a broad-based population for which testing can be available.

When a request is submitted for national coverage policy, we will review

the information that is submitted. If we believe that a benefit category exists and significant scientific evidence has been submitted, we will accept that request and post that information on the HCFA Internet site, that is, the HCFA coverage site is www.hcfa.gov/quality/8d.htm. This is an index page that hypertext links to all of the coverage decisions that we have pending and all the coverage decisions we have made in the past 18 months to two years. Probably the list of completed ones will continue to grow. We have not decided that it will be a two-year cutoff. Apparently at some point in time, we will need to stop putting items on there and create an archive people can use, but for now, you can look at all the national coverage decisions.

HCFA then will analyze the scientific information that has been submitted. It will do a literature search on its own. We use a team of physicians as well as lay staff in doing the literature search and the analysis of the information that has been submitted.

For the majority of the cases, based on our internal staff, we can make the decision whether to cover a procedure, not to cover a procedure, or to continue to allow contractor discretion because the evidence is not conclusive enough to allow us to reach a national decision, or we believe there is evidence that there is local variability that is most appropriately determined on a local level.

For a few of the situations that we have received national coverage for, we use our Medicare coverage advisory committee. It is an advisory committee similar to what this committee is. It is comprised almost entirely of physicians and doctoral level professionals. We do have a consumer representative and an industry representative on each of our panels. The panels tend to be item-specific. We have a medical-surgical panel, we have a diagnostic panel, so they are comprised of the professionals who have

expertise in that area.

The meetings are open to the public. They are announced in the Federal Register, similar to these meetings, and transcripts are made of the meetings and posted on the Internet.

Medicare, because of the reasonable and necessary provision, does not cover investigational services. However, the routine cost of investigational services may be covered for patients who are participating in approved clinical trials. The routine costs do not include the experimental item or any protocol-induced services, but we will continue to pay for otherwise-covered Medicare benefits that are associated around the administration of the investigational item or service.

The criteria that we have for Medicare coverage of routine services in clinical trials includes that the item or service must be within a Medicare benefit category. The trial also must have a therapeutic intent. We don't approve routine costs associated with any toxicity or pathophysiology trials. This generally would limit Medicare routine costs in trials to generally phase III or higher trials.

For therapeutic interventions, the trial must enroll patients with a diagnosed disease, rather than healthy volunteers. But however, for diagnostic interventions, they may enroll healthy patients in order to develop a control group.

Trials must have the principal purpose to test and improve health outcomes. This gets again to the difference we had with clinical utility, and we don't have clinical validity as part of our coverage criteria. So we are looking at changes in health outcomes. The trial must be well supported by science or it must test a service that is already in common clinical use. The trial can't duplicate existing studies, and a trial

design needs to be appropriate to answer a research question.

The trial needs to be sponsored by a credible organization or a capable individual. The trial needs to be in compliance with Federal regulations related to protection of human subjects, and it needs to be conducted in accordance to standards of scientific integrity.

In our coverage decision on trials, we deemed a number of trials to meet these approval criteria. Those are trials that are funded by NIH, the CDC, the Agency for Health Care Research and Quality, HCFA, the Department of Defense, and the Veterans Administration. Trials that are supported by centers or cooperative groups that are funded by the above agencies also are considered deemed trials. Trials that are conducted under an IND review by the FDA are considered deemed, and trials that are exempt from an IND for humanitarian reasons may be covered.

The current experience with the Medicare program with regard to genetic testing has resulted in payment during 1999 of approximately 204,000 claims for genetic tests, and resulted in $4.4 million in Medicare reimbursements.

What are our future expectations under Medicare? As genetic tests become a standard of care, we anticipate increased coverage under Medicare, but without changes in the law related to screening services, HCFA will not be able to cover predictive genetic testing or primary screening. The results of genetic testing will not affect Medicare benefits. So if a beneficiary were to receive genetic testing that indicated that they were having a genetic predisposition to a certain disease, it would not alter their Medicare benefits which they were otherwise entitled to. It would not in any way influence their access to care or alter the premiums that they pay.

DR. LEWIS: Are you almost ready to wrap up? Because I want to keep track of the time.

MS. SHERIDAN: Sorry. The Medicaid program as I said is a federal-state partnership. They provide care primarily to the aged, blind, disabled, and children and families with dependent children, and they pay for health care for approximately 33.4 million Americans. The Medicare law includes a mandatory benefit program that all states must cover, but states can add additional benefits to their program at the same financial participation rate.

There is considerable variability among the state Medicaid programs. For laboratory services under Medicaid, they must meet the following conditions for coverage. The lab must have an appropriate CLIA certification for the test. The service must comply with the state guideline for medical necessity, and health care providers must be certified or licensed in order to provide the specific type of genetic test.

Genetic testing is not a mandatory benefit under Medicaid. States determine coverage for their individual plans, and states do not report nationally details on their coverage criteria they use, so we don't have much information to share with you on Medicaid.

Thank you.

DR. LEWIS: Thank you so much. Are there any questions that are of an immediate nature to Ms. Sheridan, or can we hold questions to the end?

Our next presenter is Dr. David Witt. Dr. Witt is a medical geneticist at Kaiser Permanente in San Jose, California, and his clinical practice includes a broad spectrum of prenatal, pediatric, and adult medical genetics. He is also the director of the

Kaiser Permanente regional Huntington's disease predictive testing program. He is widely recognized for his work on population screening for cystic fibrosis, and is an international authority of Noonan's syndrome.

Dr. Witt has lectured frequently on the role of medical genetic services in managed care. Dr. Witt, thank you for coming this morning.

DR. WITT: Thank you, Dr. Lewis. I thank the Committee for inviting me here today to participate in your deliberations.

I am sure everybody here knows that managed care has dramatically changed the practice of medicine. No doubt, this will continue to expand well into the 21st century. At the same time, as you also know, medical genetics has really exploded onto the scene, and is becoming integrated into the health care delivery system as never before, and promises to revolutionize the diagnosis of human disease. So these two forces are coming together and on a collision course, and they both need to find a way to coexist.

I personally have a strong believe in the value of and importance of genetics and genetic counseling. I have been fortunate to work as a full-time geneticist for the last 15 years in a managed care organization that really supports genetic services. I have always felt that the Kaiser Permanente Northern California program can really serve as a model for the delivery of genetic services.

Today, I want to make one caveat. When I am speaking about this, I am really focusing on the Northern California Kaiser program. There are genetic services in the other West Coast Kaisers, particularly in Southern California, but they are organized somewhat differently and have somewhat different approaches to coverage, and so on.

Outside of the West Coast, the other Kaiser regions do not have internal genetic services. They are more like non-Kaiser HMOs in that sense.

So what I am going to do today is focus on three different sections. The first, just briefly, I wanted to make a few comments about genetics and managed care in general. In the second phase, I wanted to discuss and review the Kaiser Permanente Northern California genetics program, the kinds of services we have and how we deliver that. Lastly, to focus on the main thrust for today's meeting, which is looking at the decision-making processes that are in place regarding the offering and the coverage of genetic testing.

I laid out some simple points about the genetics and managed care that, if you have heard me speak before, I have gone over. I think these are five major reasons why genetics and managed care should work together very nicely.

The first is, I think basically there are parallel goals of genetics and managed care, in terms of health maintenance and disease prevention. One important point to remember that I will come back to several times during my presentation is that one of the things we do in genetics is, in our trade, is to deal with information. Sometimes it is information alone rather than genetic tests or anything that is going to directly change intervention for our patient. Information and the value to that patient can be a very important service in and of itself.

There are all kinds of examples of how genetics helps to maintain health and improve health. A baby that is born with multiple congenital anomalies, one of the things geneticists do besides make a diagnosis is to gather up information about what are the needs for that child. If there is indication of hearing loss, we will pursue that

evaluation and arrange for intervention. If it looks like there is kidney abnormalities, we will pursue that and undergo testing and recommendations for management, and so on and so forth, for the ultimate benefit of that child to improve his or her health outcomes.

Disease prevention, many examples. Hemochromatosis screening would be an example where we can actually prevent morbidity and mortality from a disease by early intervention. The whole area of prenatal diagnosis can be looked at as a way of disease prevention.

I don't think anyone here would doubt the fact that the role of genetics in medical care and medicine is increasing at an exponential rate, and so it is not something we can turn our backs to and say it won't be a big deal. Geneticists and genetic counselors know this field, and know how to do it better than non-geneticists, and I think our rule can be certainly one as an advisory consultant, if not a primary leader in it. Again, as more and more testing becomes available, that role is not going to go away.

There is an issue about medico-legal liability, that a single wrongful birth case can pay for a whole screening program. Again, as more information comes out of the Genome Project, the opportunity for those kinds of liability issues increases daily.

The last would be patient satisfaction. We know patients are very happy and satisfied when they do have access to good genetic services. On the contrary, they are very unhappy when they can't get those services.

At the same time, there are reasons why genetics and managed care have not gotten along terribly well in some cases. First of all, the services cost money, like every other health care service. The problem is that oftentimes, that expense is perceived as being disconnected from an actual benefit, and it is difficult sometimes to measure the

outcomes that we create by the traditional methods.

Again, we have to go back to this idea about the value of information alone. An example to demonstrate this would be Huntington's disease predictive testing. It is difficult to say that there is a direct impact on health care management from the result of that testing. We can't do anything differently in terms of intervening, but on the other hand, there is a lot of value to that information for that individual, for life decision-making and planning.

I believe that oftentimes, there is the wrong definition of medical necessity. Again, we can look towards Huntington's. If you exclude any indication other than having a direct intervention in terms of health care, then we are going to miss the point of a lot of the value of genetic testing. I think you often find a lot of managed care providers as well as administrators who don't understand genetics, who are relatively new, they don't know what we are about, and so they don't know how to interpret this. You will see a lot of testing that is done inappropriately, and also testing that should be done, but isn't being done.

Genetics is often the victim of policies that restrict access to specialists, which is ironic since, although we are specialists, we are also very much generalists.

Lastly, genetic disease is often perceived as being rare, that it does not apply to the health care of the population in general, which really isn't true. I think as you know, three to five percent of newborns have a birth defect. It is the number one cause of infant mortality and therefore large health care costs. About 20 percent of the general population in the United States has a genetic or genetically-related disease, and so on and so forth. So overall, genetic disease is a very important contributor to the health care

needs of this country.

I want to spend a few minutes reviewing Kaiser Permanente and the genetics program to give you an idea of what kind of services we do have. Kaiser is a very, very large and old non-profit staff model HMO. In Northern California, we have about 200 miles of geographic coverage, which cares for three million members. We do approximately 32,000 newborn deliveries each year. That care is distributed among 19 medical centers and 16 outpatient centers, and about 4,000 physicians overall that provide that care.

The program began about 30 years ago, with its inception in a very small way, and since that time has grown to incorporate four separate departments in one regional program spread among the four cities you see listed here in Northern California. Total staff, nine medical geneticists, 45 genetic counselors -- that was the last count, anyway -- one fetal pathologist, a clinical psychologist, four Ph.D. lab directors, 10 nurse specialists, two nutritionists, and 40 or so lab technologists.

What we have done is to coordinate those programs, while autonomous but definitely linked in many ways, in terms of trying to set policies and similar service plans. We operate under one single budget. We have a computer system that runs all the demographics in all the clinical laboratory services, and is available directly to any of the providers in the program.

So we have created a very comprehensive genetics program which I think is the largest clinical and laboratory genetics service in the United States. It is integrated directly into the health care system, and produces very high quality results in a very cost conscious and effective way.

The kinds of things that we do on the clinical side are referrals that are open access policy; patients come to see us either from a referral from a physician or other health care provider, or they can contact genetics and make an appointment directly. We do the standard inpatient-outpatient evaluations, diagnosis, testing, management, counseling. We cover all prenatal, pediatric, and adult genetic services. We have about half a dozen regional multi-specialty clinics, like craniofacial and spina bifida, and we have a number of regional screening programs, the state medical marker screening, newborn screening. We do prenatal hemoglobinopathy, Tay Sachs, Canavan's, and our newest addition which will be about a year old next week, cystic fibrosis screening.

On the laboratory side, we have some very large labs that are integrated directly into the clinical genetics service, which has lots of advantages, starting with coordination from the time of specimen procurement and transport and reporting out, which leads to the ability to control the quality and ultimately, to patient satisfaction.

Our cyto lab processes about 9,000 specimens per year and does the usual kinds of things, including molecular cytogenetics. Our molecular lab does about 21,000 specimens per year. We cover I think now 21 different diagnostic tests. Our metabolic testing goes to Southern California Kaiser because they have a lab there, and in return we do their DNA specimens.

We also have a large academic bent. There is a lot of teaching and training that goes on in the region. We have residents from pediatric, OB, and pathology rotating through. We have genetic counseling students. We do a lot of teaching to our providers as well as out in the communities and to support groups and to schools and so on.

We do a fair amount of research. It is a unique opportunity, because we have a closed system, and we are able to do retrospective and prospective studies relatively easily, and so there is a lot of work done on population-based genetics and health care delivery services.

We have an inter-regional database in cooperation with the other West Coast Kaiser genetics. For example, we have 100,000 amniocentesis studies in the database with demographic data and so on.

Well, let me turn to what is the real thrust of today's question, in terms of how we make decisions about ordering genetic tests and coverage.

The Kaiser Foundation Health Plan, that is, the group that actually contains the membership, does not explicitly have any comment about genetic testing one way or the other. So the decision to offer a test is really by the individual physician. Most times, that is going to be by a medical geneticist. There are some exceptions; occasionally a neurologist will have a need or desire or order, a molecular diagnostic test, and occasionally a pediatrician, for example, but 90 percent or so, I would say, is by the medical geneticist. In fact, we have gone to great lengths to try to oversee the ordering of DNA tests by other providers, all of them done through us except when we send out for a test we don't do. So we automatically know when there is a positive result, so we take the liberty of intervening and contacting the provider, so we get our foot in the door at that point. We also try to have the specimens come through us.

When a test is offered by definition, it is a covered benefit, because we are not just a provider, we are also the insurer. When an individual physician offers a test, that means the Kaiser Health Plan is going to pay for it.

A definition or a judgment about what is a medical necessity and what is reasonable care is therefore done by the individual doctor, in this case, most of the time geneticists. But I want to point out that it is really shaped by the culture that we have developed, internal to the regional genetics program, which is the result of experience, both comments and experience among our peers. We have access to a large group of professionals within genetics, and also individual opinions. But it is important to point out that that kind of process is not a formal requisite one. It is left to the individual provider as an ad hoc kind of system. We very often run it by one of our colleagues, or perhaps at a departmental meeting we will discuss, what would you do in this case, and so on and so forth.

On occasion, we will have a formal decision-making effort about a specific item that tends to be generalized and may involve more than one patient, to set some sort of a coordinating policy. But when you get to the bottom line, it really is the individual provider who makes that decision.

I would say 90 percent of the time there is probably consensus about that, but there are always going to be exceptions. There are situations where another genetics provider ordered a test or wanted to pursue a work up that I personally wouldn't have because I didn't think it was necessary, and I know that has happened the other way around, that I have done some things where the other providers may not have done that. But the vast majority of the time, we have a culture where we agree on how we are going to do that, and it is left to the knowledge and experience of the genetics providers to do that.

Clinical validity and utility do in fact matter to a large extent when we

make these kind of assessments. We look at the sensitivity of the test and the specificity. We look at, are there other identified genes that may cause the same clinical condition; therefore, we are going to get the answer that we really want, is it going to be useful or not; what is the quality of the lab doing this kind of testing, if it is not our own; what kind of time factors are involved; are we going to get a result that is timely enough, if it is in a prenatal setting.

Then in terms of the appreciation of what that result means, what is the disease burden? Are we talking about a test that will identify whether somebody is going to have a hangnail or whether they are going to have early death from a dementia disease? What is the pretest clinical risk? Is somebody at a one in four risk or are they at a one in one thousand risk? What is the patient's perception of that burden of that particular disease, and the risk? What can the test do for you in terms of reducing that risk? Will it drop from one in four to one in a thousand, or will it go from one in a thousand down to one in 900?

What is the value of the test in terms of, is it going to give us information to be used only, or is it also going to give us information that we can intervene in that patient's management? So all these different factors go into the computer, if you will, to help us decide if we are going to offer the test or not.

The underlying guiding principle is that we want to practice good medicine and provide the highest quality medical care that we can, but do it in a cost conscious way. But certainly, cost is not the number-one priority.

We do not vary our coverage based on whether it is a diagnostic test or a predictive testing situation, and similarly, we don't change that concept, whether we are

going to be able to give information that is of value to the patient versus a direct management or intervention.

And experimental therapies and tests are excluded by the Kaiser Foundation Health Plan contract in a general sense, but certain exceptions can and are made. I think as you know, there are sometimes orphan diseases and so on, that an individual research lab may be working on. In fact, oftentimes there is no charge for that kind of a testing anyway. We have pursued it if we thought there was value for our patient. For bigger ticket items, for example, the decision to do a fetal skin biopsy in a rare disease, that does have to go through administrative approval.

In terms of FDA approval, I don't really think that would have much impact on our decision-making, because I think our own assessment would supersede whatever the FDA decided to do. And certainly, there is precedent for that, in terms of FSH testing, for example, or a lot of DNA diagnostic testing that has been around for the last five, 10 years. We don't do it just because it is not FDA approved.

The Kaiser Foundation Health Plan benefits and the premiums are not influenced by having a pre-existing genetic test result or a genetic disease per se. Like basically any other insurer, certainly the health plan can refuse membership to somebody on the basis of the fact that they have some health problems or medical disease that is going to result in very high predictive medical costs. But it is not necessarily whether it is genetic or not.

One exception I think is that Kaiser is very liberal, in the sense that if you are an individual who has the Kaiser Foundation Health Plan through your employer, then your entire family, your children and your spouse, will be covered regardless of what is

going on. So you may have four children with muscular dystrophy, and there is no question that they will be covered automatically.

So lastly, in terms of the future, I don't really expect there to be specific contract language in the health plan membership, although I suppose that could happen. I think that is probably too detailed to really be worth it. I think there may be just some general comments, but I doubt that will change very much.

But I do think that as more and more genetic tests become available, and increasingly become available to non-geneticists where we may lose some of that control, that the organization may want to set guidelines and have geneticists make specific recommendations, perhaps as more of an oversight to help the organization decide what is reasonable and what isn't. In fact, I think that would be a very good role for genetics, and something we would be very happy to take on.

So overall, I would say for managed care and genetics, the goal is to have a win-win situation that works for the genetics professionals, for the managed care organization, and especially for the patients, because we need to give them the best medical care possible.

Thank you.

DR. LEWIS: Thank you. Next we have Dr. Allan Bombard. Dr. Bombard joined Aetna U.S. Healthcare in 1998 as medical director for women's health for the Pacific and West Central regions. Dr. Bombard oversees Aetna U.S. Healthcare's women's health program related to genetic testing for breast and ovarian cancer, and he is also board certified in medical genetics, and has extensively lectured and published on women's health issues, including areas related to genetics.

Thank you for being with us this morning.

DR. BOMBARD: My pleasure. Thank you, Dr. Lewis and members of the Committee for inviting me and asking Aetna to participate in this.

I happen to be on active duty this week with the Air Force Reserve, so I would also like to thank the Department of Defense and my commander, Dr. Barry Thompson, who is a geneticist, to allow me to come and meet with you this morning. I am wearing a different uniform today.

Where to begin? I guess first, I'd like to thank David Witt and in honor of thanking him for his terrific presentation, this is a picture of Berkeley and Oakland where David works.

How does an insurer decide to cover genetic testing? I certainly can't speak for all insurers. What I am going to try to do for you today is present a picture of how Aetna makes decisions on coverage of genetics issues. Aetna is a company that sells a wide variety of health care products, not just managed care or HMO, but a variety of other non-managed products, and our policies apply to all of these different products.

I was recruited out of academics about three years ago, one of the reasons being to help bring a focus of genetics into a managed care portion of a company that did like to identify diseases and manage them actively, for example, asthma, diabetes, low back pain, congestive heart failure, diseases where a specific patient population could be identified, severity levels could be stratified, we could then identify individuals at risk and case manage them to improve outcomes. Aetna at that time had no focused program to look at the issue of genetics or genetic diseases.

So we looked to our corporate policies for implementing coverage for

specific items and apply them to genetics. In the next two slides, I list our development of coverage guideline process. As with Kaiser, we look to see that care or treatment is likely to improve the outcome and health of the member. We cover services that are related to the diagnosis of an illness, information that will ultimately affect the course of treatment and management for that member.

Care services and treatments are for health plan members, and not necessarily for the benefit of other individuals in a family. That is an issue I think that the genetics community is going to have to deal with as we go forward, genetics as a family disease.

The short answer to my presentation -- I will try to be brief, I know we are running behind time -- is that we look to relevant professional colleges for their guidelines, and use them. The challenge we have exists when the professional organizations and professional colleges differ in their recommendations; which one do you use.

At our company, the chief medical officer or the designee ultimately makes the decision to evaluate a technology. There is a process for evaluating that technology. Requests for a chief medical officer to address a policy comes from the field, from medical directors, from members, from providers in the field, whether or not an issue that has been formally evaluated.

As part of the process, a comprehensive literature search is begun. We ask for consultations from experts in the field, local, national, international occasionally. We develop draft guidelines and circulate them for review among our medical directors, and we present them for review at our regional quality advisory committee, of which there are

employer members, patient members, provider members, not necessarily all employees of the company.

Ultimately, there is a senior core policy review, and then we integrate that coverage into a coverage policy bulletin library. Currently, our coverage policy bulletins are available on the Internet. The Internet is not all it is cracked up to be in terms of rapidity. Like mailed documents, there is a lag time for approval.

For example, you have in your handouts our coverage policy bulletins related to four areas of genetic testing. None of them are current. So despite the fact that you can access the Internet relatively easily, there is a lag time between the development of new coverage, especially in an area of medicine where there is rapid change as in medical genetics. There is a process to move them to the Internet, but the Internet still is faster than the U.S. Postal Service, so it is a tack we are trying to take.

This summarizes our implementation algorithm. We look to the relevant professional colleges, we look to experts in the network, ask local providers for their input, and ultimately the guidelines are disseminated.

How about genetics? First off, we look to the peer reviewed medical literature and relevant textbooks. While we would like to put Emory and Remoyne's text of the principles and practice of medical genetics on our website as the standard, it is not practical. So the policies are distilled into broad coverage guidelines.

With respect to medical genetics, being in women's health, the three organizations that I tend to focus on for their policies are the American College of Medical Genetics, the American College of Obstetricians and Gynecologists, and the American Society of Clinical Oncology.

An example of the conflict in women's health, breast and ovarian screening. Does one turn to the ACMG for their guidelines because there are genetics issues? Does one look to ACOG policies because there are women's health issues? Does one look to ASCO because it is an oncology issue? We look to the government agencies and Medicare, but in the main, since most of our members are employees and of commercial age, much of Medicare policies don't apply to younger women. In fact, the Medicare policies have not yet completely addressed the issue of preventive testing, which is where we feel the great benefit of genetics is.

Now, coverage of genetics services are not new. Rhesus testing, Rh testing in pregnancy, has been done for 40 years. HLA analysis is a covered benefit. It is a genetic test, we use it in immunology and transplant. In pregnancy, there are common standard diseases that we offer genetic testing screening for, Tay-Sachs disease, and enzymatic-based tests hexosaminidase-A, cystic fibrosis, hemoglobinopathies and multiple marker testing such as the triple test or quad test that are available as routine screening tests in pregnancy. There are genetic tests out there, they have been supported by the professional colleges, and we cover them.

With the fruits of the Human Genome Project becoming available, we are now having to look at other, newer genetic tests and finding ways to implement coverage for them. We have a formal program for looking at breast and ovarian cancer screening in high-risk families. We work with the American Medical Association to develop a CME monograph for providers, and we have developed a process whereby if members at increased risk meet the coverage criteria that we have established, testing is covered, and we don't get the results of the testing, which addresses the issue of confidentiality and

concern about discrimination on the basis of genetic information.

As an aside, since the American Society of Human Genetics meeting two weeks ago or three weeks ago, we have adopted the ACMG guidelines as a standard for covering BRCA. We are looking to develop a similar program for colon cancer when the CDC recommendations are put in print for hemochromatosis.

In essence, for BRCA, we look to risk assessment using the published algorithms. Again, we feel that the ACMG is the most comprehensive, and so we have adopted that as our coverage guidelines.

In association with that and in terms of medical documentation, we look to a three-generation pedigree. For us, it is a way to formally promote -- push, if you will, genetic counseling. We cover genetic counseling. We feel it is incredibly important. We cannot mandate it, because there are areas in the country where genetic counseling is not available, and so we look to include as much genetic counseling information in the process.

Fundamentally, BRCA analysis is covered when the risk to have a mutation in a high-risk individual is greater than 10 percent. That is directly out of the ASCO guidelines. In fact, the 10 percent risk is the threshold for the ACMG criteria. So there is some consistency.

Information that is obtained must be used in the management and care of the member.

Now, it does present a little bit of a problem, because genetics as I said is a family-based medicine. Using breast and ovarian cancer as an example again, there are instances when it is critically important to look at a molecular mutation in another family

member to make a decision about what is the appropriate medical treatment for the person that is sitting in front of you.

Many times, that other family member is not one of our insureds. We have a fiduciary responsibility with our employers to only cover medically necessary services for our insureds. However, because this information is critical many times to making a decision on how our covered member will be treated, we would cover the testing in that non-Aetna member, assuming that their insurer doesn't cover that testing.

As I said, there are a number of genetics-related policy bulletins that are available for review. I would be happy to make available the most current CPBs once they are available for publication on the Internet. I can send them to Suzanne Goodwin.

As I said earlier, the development of coverage policy guidelines is a fluid process, and it is made more difficult with the rapid advances in genetics. We have recently initiated a mailing to all of our providers who have ordered a genetic and molecular test for BRCA for one of their members in the past that had the service denied because it didn't meet the coverage criteria. The coverage criteria have changed, and so we are in the process of case managing those members, if you will, by mailing a letter to each of those providers saying the coverage guidelines have changed, here is a copy of the new coverage guidelines. If your member meets the new criteria, please consider submitting for the reimbursement of that test.

Just to close, we currently have approximately 19 million members across the country, so for me it has been a professional and personal challenge to develop a genetics policy that is applicable across medical practices across the country. I don't see another way to do that without relying on national professional colleges as your standard.

Moreover, we have to look to application of coverage in a wide variety of health care products, not just managed care products, the HMO that you would see at Kaiser or in the Department of Defense, but non-managed products as well.

I've done my best to keep to my limited time, and I would be happy to take any questions.

DR. LEWIS: Thank you so much. Why don't we wait and do questions all together at the end.

Our next presenter is Dr. Victor Villagra. Dr. Villagra is president of quality and strategic medical affairs at CIGNA Healthcare. He is responsible for strategic planning and oversight of all national quality improvement initiatives and disease management programs. He is also the corporate head of the CIGNA Technology Assessment Council and the Health Promotion Disease Prevention Council. He serves on numerous national advisory boards and lectures in the area of disease management, technology assessment, quality improvement, and preventive medicine, and is a board-certified internist and a fellow of the American College of Physicians.

Thank you, sir, for being with us this morning.

DR. VILLAGRA: Thank you very much for inviting me to participate in this Advisory Committee. What I will do is, I will go over CIGNA's approach to genetic testing as part of a large technology assessment, the incorporation of new technologies into our benefit portfolio, and give you a general overview of how we make coverage decisions.

The first thing I had to ponder for awhile in preparing for this session today is what exactly constitutes a genetic test. Understanding that molecular genetics

and the methodology really spans a whole spectrum of possible tests, I used the general guidance of genetic tests as being those that have been incorporated in some legislative language, for example, in the state of Arizona, as a general guideline. I think with that approach, I will be in the ballpark of what you wanted me to talk about.

I decided to cover these four points: exactly what is covered, how is coverage decided, how is a test paid for, and then talk about some open issues and concerns that we have on an ongoing basis.

Covered tests are no different than some of the ones covered by other insurance companies and exemplified in previous presentations. They span both prenatal testing, newborn screening tests, susceptibility tests, and then a variety of genetic tests on symptomatic individuals who have a variety of medical conditions.

When a genetic test exists as opposed to a new one that has been approved by a regulatory agency, the process is roughly as outlined here. An individual physician may request a genetic test. Our clinical staff evaluates that request, establishes if there is an explicit policy for coverage and reimbursement for such a test. If the answer is yes, then the next step is to go into a detailed set of guidelines that, in our case is also the compilation of various sources, professional organizations, public domain information, as well as reviews of the medical literature conducted by not-for-profit or privately owned technology assessment companies.

Following this process, there is a process of approval that also goes through the appropriate medical necessity criteria and so forth. If there is no policy, and that is increasingly the case with the advent of new tests, there may have been individual requests in the past, and we may have adjudicated that particular request in some fashion.

The old CIGNA health plans -- and we have a presence in all states and in Puerto Rico -- log in particular decisions made with requests for any new technology for which there is no policy. So we have a pretty good idea of when a request arrives in Florida, what the decision may have been in California or may have been in other states. It is not a 100 percent tight, but through the incorporation and the logging of these requests, the scientific literature research that follows the decision, we try to maintain consistency in the adjudication of cases in the evaluation of technology, so that we build upon what has been done before.

If there is no precedent, and this constitutes an absolutely new request for something that just appeared, then a team of clinicians versed in the clinical appraisal of medical literature then evaluate the particular request. As you can see, all of these pathways not only create and build up precedent and, if you wish, a library of scientific evidence and opinions in an iterative fashion that spreads the entire company, and ends up in the application of what we think are appropriate utilizations of new technologies and coverage decisions.

The guidelines developed by CIGNA staff is again a blend of opinions from professional organizations and the peer review literature that has a specific format where a description of a test, the conditions under which it might be requested, what are the CPT ICD-9 codes that apply to this particular request, what are the approval criteria, what are the definitions in terms of medical necessity.

In this particular chapter, we also include state-specific language, maybe not for genetic testing; I'm not familiar with any stat- specific mandates for example for coverage of either genetic tests or counseling, but in general for any new technology for

which there may be state mandates, then the guideline incorporates in its text a description of what the law requires in that particular state. It applies to fully-insured HMO products that are under state department of insurance jurisdiction. So this is tracked in a sequential basis, and then, at the end of course, a comprehensive reference list that justifies our particular position in terms of appropriate utilization and coverage.

Like our colleagues from Aetna, we too rely heavily on professional organizations in terms of determining coverage policy.

This diagram defines at a very high level how we approach new technologies, in this case genetic testing. Through an informal process of ongoing communication with over 120 medical directors who are operating at the various health plans in all states, and through the surveillance of the medical literature in this area, we identify genetic tests for example that have the potential for improving health outcomes. We also detect high provider interest by simply the number of requests that we begin to get from the field, and at times there is high public or member interest, either through individuals who raise the issue or through advocacy organizations with whom we maintain very close contact, just so that we know what the needs of our constituency might be.

On the left-hand side of that diagram, the description of how we determine policy, whenever possible -- and almost always, this is possible -- we request input from a technology assessment organization such as Blue Cross and Blue Shield Technology Evaluation Center, or if they are a public domain, technology evaluations that provide independent -- and that green band is meant to represent an independent review process -- then we use that independent review as a source of objective information.

This is coupled with the research that is done internally by the technology assessment council, which is made up of 16 physicians representing various specialties with interest and experience in critical appraisal of medical literature research methods and so forth. Through this process, CIGNA policy for coverage, coverage with certain conditions, which is almost always the case, or no coverage, is determined.

That information is logged into a computer system, an internal online system that disseminates the information throughout the company.

We like the ED criteria for establishing new test coverage or the coverage of new technologies. The five criteria are that it must have final regulatory approval, that the evidence must permit conclusion, that the technology must improve the net health outcome, that the technology must be as beneficial as any established alternative, and that it should be available outside of the investigational setting.

You have to remember that our constituency, our customers, are large, multi-site, self-insured companies that put a premium on consistency in the adjudication of benefits throughout the country. Federal Express employees, for example, working in New York City, working in Miami, or working on the West Coast, communicate with each other and the management of that company would like to see that we have a process by which we can extend consistency throughout the country with of course appropriate respect for differences in local mandates and things of that sort.

But that is the process on the company policy side. On the individual case, for new tests, for new requests for which we may not have clinical expertise within the company, we again rely on external opinions. We send these cases to a national expert chosen by the medical care ombudsman program, or by the Hayes organization that has a

roster of hundreds of national experts, credentialed, who are picked independently from us. We simply say, we would like you to review a request for this particular benefit.

These intermediaries working on behalf of that request choose an expert. A medical opinion or recommendation is rendered, and the company essentially follows through with that recommendation. Occasionally there may be clashes with actual benefit language in which we have to negotiate coverage of these decisions on an exception basis, based on the appropriateness of the medical indication.

That decision, as opposed to being made on a company-wide level of course, is made by the medical director of the health plan. As I mentioned before, aiming for consistency, a process of tracking these decisions.

Finally, how are genetic tests paid for? This is a very complicated subject, and I cannot do it justice. But I will tell you in very general terms how it happens.

We have national contracts, capitated contracts with two or three large laboratories. Quest Laboratories, LabCorps, and Smith-Kline Beecham are still doing some laboratory tests. All of these national vendors offer genetic testing, and they cover 70 percent of the tests that we would deem genetic tests throughout the country.

In cases where we have guidelines and prior authorization requirements as I described before, that process is followed at the time of the request for the tests. I mentioned how new tests are added. Essentially, the majority of not all of the genetic tests offered by one of these vendors who are old tests, shall we say, are covered benefits.

Occasionally, not occasionally, significantly, and in a scattered fashion throughout the country, we have capitated contracts with hospitals or multi-specialty group practice, for example, that have their own laboratories or who have established

relationships in that community with a reference laboratory.

In these cases, the prior authorization in the clinical guidelines also apply, although we have less control over the actual application of these guidelines. As you can imagine, the application and actual use of the genetic tests in the hospital setting is pretty much dependent on the physician's request and the need for that particular test to occur.

Having capitated that hospital or paid the hospital on a case-based rate per diem basis where we lose the detail, then there is no specific control mechanism where we can look for appropriateness of utilization. So you have to consider that as a special case.

Then at the other end of the spectrum, we also offer non-managed care products, PPO and indemnity products, in which case the tests are also covered and reimbursed on a fee-for-service basis. They track individual CPT codes, generally speaking.

These for us are easier to monitor, because essentially the facility of the providers are not reimbursed until a detailed bill or claim is submitted. That detail then exists, and we can track it through claims, as I explain at the bottom.

The other side, when we are dealing with capitated contracts, the tests essentially have been paid for. Only the work flow processes that look at appropriateness of testing is the best way that we have to track the utilization of these tests. If the providers give us information about what tests have been done, and with the national contracts we have very good information about encounters as opposed to claims, then that is a way in which we can profile what the utilization of these genetic tests are.

For example, I did a query of genetic tests that may have been done in the

past year in a couple of our products, and we had over 43,000 of these.

So this is a very general overview. Many questions pertaining to the appropriateness of the delivery system for managing informed consent, pre-testing counseling, post-testing counseling are very real for us. I am running out of time, so I am not going to elaborate on that. I'll be happy to answer questions later.

Thank you.

DR. LEWIS: Thank you. Our fifth presenter this morning is Mr. Cecil Bykerk. Mr. Bykerk is Executive Vice President and Chief Actuary of the Corporate Actuarial and Strategy Planning Operation at Mutual of Omaha. His duties involve actuarial oversight, planning and acquisitions. In addition, he is responsible for asset and liability management, a component of the corporate risk management. He currently serves on the board of trustees of the American Academy of Actuaries, as well as the Risk Classification Committee and its Task Force on Genetic Testing and Health Insurance.

Recently, he was named chair of the insurance subcommittee of the National Conference of State Legislatures' blue ribbon panel on genetic technologies, as well as chair of a newly formed Task Force on Genetic Issues of the Health Insurance Association of America.

Thank you for being with us this morning.

MR. BYKERK: Thank you very much. Thank you for giving me the opportunity to come and speak with you. You have heard four presentations already this morning. Some of what I would have said overlaps, and so I am going to focus on some of the differences. I'm going to be speaking to you today regarding indemnity insurance, primarily focused on individual policies, and to some extent insured group policies, and

I'll point out a couple of differences there. I will try and differentiate between the managed care elements which some of the previous presenters talked about, and how indemnity insurance is handled.

First of all, with respect to determining the coverage policies, it is really driven by the policy or contract language. As was mentioned earlier, primarily medical necessity, not experimental or investigative. We look at the state contract provisions and any mandated benefits that are required by a given state.

Ultimately, the medical directors of the company make the decision with respect to whether something will be covered or paid for. One difference with respect to group contracts is that the employers do have a role in setting the contract and what they are willing to pay for. Individual contracts are developed by the company and issued as such with no variations other than some limited number of riders that can be added.

One rider that I might mention that is commonly available with individual coverage has to do with adding features that would include preventive medicine. Most individual-based contracts don't really cover preventive-type coverage, routine physical exams, et cetera, but in the case the individuals can add a rider that would provide for co-pay visits and usually in that case, preventive medicine or routine physicals and similar types of things would be covered.

With respect to how we then determine what actually would get covered, interpreting the contract language, we have extensive files that help determine the medical necessity. We have information provided by technology personnel within our companies, as well as what we can glean from outside. We review the medical literature and of course FDA recommendations and approvals are important.

With respect to whether or not we have -- and I'm going to focus on Mutual of Omaha right now as an example of an individual carrier in the marketplace. Mutual does not have a specific set of genetic testing guidelines, as opposed to some of the previous speakers' companies. Our feeling is that there is too much fluctuation in genetic testing technology today. We don't really have the desire to promulgate and immediately and repeatedly have to revise it. So we have not established that kind of formal practice.

I might also mention that with respect to the individual market, we really haven't had a large number of requests for genetic tests, for reimbursement for genetic tests. I say that, and I need to caveat it by saying there are, as was listed in one of the previous presentations, a number of genetic tests that have been historically given in the case of pregnancy and childbirth that are genetic tests, and we routinely cover them, but we have sort of lost track that they are really genetic tests.

In lieu of a formal policy, we require the tests to meet policy definitions, medical necessity, necessary and reasonable, FDA approval. For screening purposes, we would only cover it when the signs and symptoms support the need for the test, and something that is extremely significant and important to our decision to cover something is the ability to impact a future outcome.

In the actual handling of a case, since we don't have a formal policy written, if it is clear from previous examples, previous cases, the medical review nurse supervisor can approve coverage. If it is not clear and not straightforward, it would be referred to the medical director. Denials are always made by a physician, typically the medical director. We don't have low-level clerical people making denials of requests.

Finally, the medical director may seek consultation from outside the companies in some cases.

As far as the role of physician and/or the patient, a request must be made with an explanation of why they are requesting it. There must be demonstration of high-risk clinical history or demonstration of signs and symptoms.

In the material that was handed out to you -- and I'm not going to take the time to go through it, you can read through it, I did ask one of the committees of the Health Insurance Association of America to do a survey for today's presentation. That survey and a short synopsis of it was handed out. I can provide more copies of that if we need.

The survey, I would just add, other than what is written there already, there were eight respondents. The companies that responded are medium-sized, individual indemnity-type companies. They are not the large managed care type companies. You can see that the specifics with respect to their answers are somewhat of a wide range. On the other hand, there is a fairly consistent pattern that these companies don't have big genetic areas within the company, and function very similar to my company.

In your material I have actually provided a typical definition of medical necessity. For the sake of time here, I am not going to read these slides, but you can see how the typical individual contract defines medical necessity. A group insured contract would be generally similarly defined.

There is the other two bullets for medical necessity. Also I provided the definition for experimental and investigative. Then finally, reasonable and necessary, and you can read those or look at them at a later time.

Now, with respect to reimbursement during research phases, generally we don't reimburse for things if it is not FDA approved. If it would be approved by the FDA but it is still in a research phase, consideration depends on determination of whether the test is reasonable and necessary. This all sounds like a big circle here, but you have to go back and look at that definition and see how that fits in.

Again, we receive very few requests for, I would say, emerging genetic tests. Some of the more common tests that have been used for years, we do, but the more emerging tests we receive very few, but of those we approve about half of them. Experimental genetic tests are generally not covered.

The role of clinical validity and utility. If it is useful and valid, it is likely eligible, if the performance of the test is reasonable and necessary, and if it would be FDA approved.

With respect to whether FDA approval of genetic tests would be helpful, our feeling would be that it would be extremely helpful to our companies in making decisions about these tests. We generally don't pay for genetic tests or other similar types of things if it is not FDA approved. Our policy language excludes experimental or investigative services, although we do make exceptions, and circumstances can result in coverage, even though it is not technically covered in the contract if we feel there is medical necessity and it has been demonstrated.

Again, we receive very few requests. We pay about half of them. With respect to measurement, we do not have a measurement system in place at the current time. We review that periodically, as we did just within the last couple of months. We don't feel at this point the mechanics of the requirement justifies the expenditure, given

the number of tests that we have. When that goes up, we will add a measurement system.

Diagnostic versus predicative. We are more likely to pay for diagnostic than predictive, again going back to the issue I mentioned earlier. Preventive services are typically not paid for, routine physicals, et cetera. Predictive types of tests would tend to fall in those kinds of things. If a person has a rider that covers that, or if the base contract covers it in the case of a group contract, then it would be more likely that we would pay the predictive tests as well. We have paid for both, but again, absence of an available treatment program would weigh heavily against paying for it.

Looking toward the future, as tests become more common and part of the standard clinical practice with more utility and validity, development of specific criteria and/or a policy would be indicated. We expect that increased demand for testing, and at lower cost and more availability would require an articulated policy. But we also know that there are many complex legal and ethical issues to be dealt with here.

One last question that we talked about, and I added in a couple of slides here. That has to do not with reimbursement for genetic tests, but what is the impact on the business relative to first knowledge of genetic tests having been given to an individual, how does that affect things.

There is really no effect -- if we know that somebody had genetic tests, there is no effect on the premium benefits or access to the coverage. In the case of group coverage, the HIPAA law would prohibit that. It is the guarantee issue, and so we can't do that and can't vary the premium on that basis. There is a specific part of the law that says in the case of group coverage, you can't reflect genetic tests.

In the case of individual business, HIPAA does not specifically apply to

individual business. However, there is no evidence that any insurers are using it at the current time. There is a recent paper by Mark Hall, I think he is from the Medical University of Wake Forest, I can get you the citation if you are interested in that. But he did an extensive research project, and essentially found no evidence of individual insurers using genetic tests with respect to benefits, premiums, or coverage.

Our question is, are they sick now, not are they going to get sick in the future. We know that everybody will get sick in the future if they live long enough. The question is, are they sick now. That is all we are concerned about.

With respect to knowledge of a person being at risk for genetic disease, this is slightly different than the effect of just having knowledge that someone took a test. The same comments as the previous slide, except for the question of pre-existing conditions.

With group, again it is largely prohibited unless the person would be in a symptomatic situation, showing evidence of the disease. In the individual market, it is not prohibited per se, but in practice there is no effect again unless there is symptomatic evidence of the disease being present.

I would add here, as you go into your deliberations about various things related to genetic testing and genetic flaws and so on, down the road, I think there is going to be a very significant question that we are all are going to have to answer in the insurance industry and medical community – when does a genetic flaw become a re-existing condition. I think right now we say they are symptomatic or not symptomatic. Looking out in the future five or ten years, I think that dividing line is going to fuzz together. I think it is going to be very difficult to say this is a pre-existing condition or

this isn't a pre-existing condition. So that is one thing that I would suggest that further thought might be given to how we are going to deal with that question.

Thank you very much.

DR. LEWIS: Thank you. I'd like to thank all of our presenters for coming this morning and providing us with a better understanding of the reimbursement policies and practices of their respective organizations regarding genetic test services.

Now I would like to move to a roundtable discussion with the presenters and Committee members on reimbursement policies and practices, as well as any issues or comments that stem from the background we have just heard.

DR. BURKE: I'd just like to make a comment for clarification. That is, I believe SAGCT has used the same definition of clinical utility that Medicare uses. I think we distinguish between clinical validity and clinical utility and define clinical utility as related to changes in health outcome as a result of interventions after testing.

MR. HILLBACK: I just had a couple of questions from the last presentation. Since home brew tests, which are still the majority of tests, aren't currently approved by FDA, does that mean that you don't consider them because they are home brew, or because they have no approval process at all, you have to look at each incident?

MR. BYKERK: I would say that since most are in that category, we don't automatically not cover them, but we would have to look at each case on a case-by-case basis and decide if there is enough evidence or symptoms or other factors that suggest that even in the case that it is not FDA approved and it is a home brew, that we would still feel like it would be beneficial for the individual to have the test.

MR. HILLBACK: Just a second clarification. A couple of slides later,

you talked about demonstration of risk or signs and symptoms. You didn't mention family history as part of that. Is that a pretty crucial factor in determining usefulness?

MR. BYKERK: Family history in certain circumstances would clearly be something that we would be looking for in that general category of signs and symptoms.

DR. PURYEAR: I have a question for HCFA. Given that there is a new bill that has been signed that is entitled Screening for Heritable Disorders for Infants and Children, do you think HCFA is going to broaden its definition of genetic testing to be more in line with that definition that was recommended by this body and the Public Health Service Task Force on Genetic Testing to at least include the four million infants that are screened each year in this country, in the newborn screening programs?

MS. SHERIDAN: I'm sorry, I work on the Medicare side of the house, so I don't have a lot of experience with the infant-children program, and I am not able to respond to that. Perhaps Jeff might have some ideas.

DR. KANG: This is for a Medicaid bill? That is the only question, really. If this is for Medicaid, and it is a mandatory federal benefit, then all 50 states must cover that. So the question is -- I'm not familiar with the bill, but the question is what is the bill and is it directed to Medicaid.

DR. PURYEAR: It is also how you define genetic testing. If you know it to be just DNA-based testing, then you are excluding the testing that is currently going on in newborn screening programs.

DR. KANG: I'm sorry, in order to answer the question, I need to understand what is in the bill. This is what is awkward about both Medicaid and Medicare programs, is that the benefits are statutorily legislated. On the Medicare side,

for example, they do it by exclusion, or things are excluded.

So for example, oral drugs. We all know oral drugs work, but it requires legislation to get that added to the Medicare benefit. The other thing is, we had to get flu shots added to the Medicare benefit by statute. It is a very archaic program, quite frankly. I hate to be saying this, as someone who is running Medicare.

On the Medicaid side, the way this works is, the federal government can mandate through legislation minimum benefits that all states must meet, and then states can exceed that, if they wish. So the issue here is, I don't know what they are asking for here, but this is all statutory. So I just need to understand the legislation.

MS. BOLDT: (Comments off mike.)

DR. BOMBARD: We are very strongly supportive of genetic counseling, whether it is done by genetic counselors, big G, big C, or genetic counseling as a generic process.

In the main, our contracted providers, our network providers, are physicians, and we pay by CPT code for the level of service that is provided. So in the main, physicians that are providing genetic counseling, whether they do it themselves or whether they have on their team a genetic counselor, they bill under one of the relevant CPT codes. It is usually, if my memory serves, 99243.

So we look to the credentials of the provider who may become participating in the network. At present, genetic counselors in most states don't have licenses to practice, though that is changing. In the main they don't have malpractice liability insurance, all of which are required for any network contracted provider in a network benefit, without making this whole issue too complex.

DR. LEWIS: Could I just follow up on that with Ms. Sheridan for one second, and ask you, under Medicare-Medicaid, whether or not the “incident to” law -- how do you deal with reimbursement to non-physician providers, for example, genetic counselors, clinical nurse specialists? I know that has been an issue for those of us who aren't physicians. How would that be applied with genetic counseling?

MS. SHERIDAN: The Medicare law does provide for coverage of services that are incident to physician services. That person who is providing the incident-to service can be a nurse, can be any kind of non-physician practitioner who is in the employ of the physician and the physician does the billing.

The Medicare law also allows independent billing of nurse practitioners, physician assistants, and clinical social workers, clinical psychologists, to the extent that they are operating within their state scope of practice.

DR. LEWIS: But not genetic counselors?

MS. SHERIDAN: Genetic counselors is not specifically identified.

DR. KANG: Just to be clear, you would need a statutory change to get that added.

DR. CHARACHE: I am looking at two questions that came through from a number of presenters. One is the question of FDA approval of the test that was touched on a moment ago, and the other is the definition of medical necessity. I wonder if we could take an example, I thought perhaps hemochromatosis, in which the patient is well, but there is a strong family history of the disorder.

My question is, do you have to wait until the patient or the individual who has a given policy to develop symptoms of hemochromatosis before you would get

reimbursement for the test? Or can you do it prospectively and prevent that patient from ever getting symptoms, that healthy individual?

The second question is, since that test is not FDA approved, would that be reimbursed? Again, it is the issue of the home brew, as so many of the genetic tests are.

So I am wondering first about the Medicare issue of that, and then how this would be handled according to policy by the different people who are helping educate us?

MS. SHERIDAN: From the Medicare standpoint, the FDA application is only in terms of whether FDA approval is required for marketing of the drug. So home brewed tests which are not regulated by the FDA, we don't look to the FDA with regard to those particular tests.

But with regard to the primary screening, in the absence of signs, symptoms or personal history of the disease, probably most of our contractors would deny the test based on the screening exclusion.

DR. KANG: But the question you posed was if they had a family history of hemochromatosis.

DR. CHARACHE: Right, they have a family history but they are asymptomatic themselves.

DR. KANG: I would say that that would be part of their personal history and ought to be covered.

DR. CHARACHE: So you are saying it ought to be covered and you are saying it is not.

DR. KANG: I just want to be clear, I'm not sure she understood the

question, but you have the family history, I would say that it is the personal history, and that would be covered.

I would like to make just one other comment on the FDA issue. To the extent that we found the home brew lab with severe analytic validity problems or clinical validity problems, our view actually would be that we would be interested in non-covering.

So this gets to some of your issues that I think you have to deal with here. Just because FDA has taken a pass, we as a purchaser would be interested in making sure that there is appropriate analytical and clinical validity of the test. To the extent that the information comes to light, we would have some problems with that.

DR. LEWIS: Dr. Villagra, you were going to respond?

DR. VILLAGRA: I was going to address the issue of the symptom threshold as a criterion for coverage. In our case, it is certainly not the operative criterion.

You can argue that high cholesterol is not a disease in its own right, it is just a phenomenon defined as pathological at a certain level, but it produces no symptoms, and if left untreated some people will develop coronary artery disease and so forth.

You can argue that colonic polyps that are discovered with a colonoscopy are asymptomatic. So in terms of creating coverage policy using symptoms as an explicit criteria, I would find that very difficult to operationalize, because of those types of more mundane situations that we encounter every day.

With respect to the issue of FDA approval or CLIA or other regulatory body, our interest is like expressed by the Medicare colleagues, is to make sure that

appropriate execution of the test in terms of its validity or reliability and predictive values are under some sort of oversight, and that we can have assurances that our members receiving these tests are receiving a good service. So that would be the criterion and the proxy for that is regulatory approval, generally speaking.

DR. CHARACHE: I should have said signs or symptoms of disease. You have mentioned signs of disease, but I am talking about someone who is totally healthy and you don't know whether he is going to develop a fatal outcome or not unless you have the test.

DR. WITT: I think that is a great example, because it brings into focus some of the issues that have been mentioned during the presentations. I think that would be a very appropriate referral to genetics, having a family history and nothing more than that. But then we have to clarify what is a family history. Clearly, that would be appropriate for a sibling of an affected individual, that is a 25 percent risk, and even to a child, even to an adult child of an affected individual, where the risk may be five percent or so. But when you start getting third degree relatives and such, you might say that is not a high enough risk.

But family history in a general sense is a perfectly appropriate referral reason for genetic services. The other element here is, in addition to counseling, what kind of testing. It brings to bear the question about what is a genetic test. In most of these individuals, the most appropriate place to start is by chemical testing through iron saturation studies and so on, not molecular testing. They may have had that before they got to genetics, but that certainly would be an appropriate place to start with a reasonable a priori risk, and then go on to molecular testing if it is going to be helpful for clarifying

the situation.

DR. CHARACHE: And the FDA approval requirement?

DR. WITT: Doesn't bother me.

DR. MC CABE: I had a couple of questions. I guess we are playing on the FDA thing because it is part of the recommendations. Mine was a follow up to Mr. Bykerk on this follow up to Elliott's comment.

You had said that for home brews that were not FDA approved, that it would be on a case-by-case basis. If home brews came under FDA review and now were reviewed and approved, would that facilitate the decision-making?

MR. BYKERK: Discussions with our medical directors would -- the answer would be yes, that would help our decision-making process. That would not be the sole criteria. We would still need some grounds for medical necessity, et cetera, but having an FDA-approved test would give us some comfort in making that ultimately decision, yes.

DR. MC CABE: I had a couple of questions for Ms. Sheridan. Medicare uses the criterion for reasonable and necessary. FDA has statutory authority, their language is safe and effective. Is there any possibility of bringing these together some way? Because it seems that the language, while being relatively -- it is four words that are different, but it creates a huge abyss between decision-making in these two agencies. Is there any possibility that the two agencies ever come to agreement on the criteria, both having to do with the practice of medicine and clinical utility?

MS. SHERIDAN: It is my understanding that the FDA's definition of safe and effective basically looks at, does an item or service do what it purports to do. We

use, as I mentioned in my report, a health outcomes view of efficacy as opposed to effectiveness in determining reasonable and necessary.

When we look to FDA for the clinical validity, so to speak, portion of it, if it goes to the issue of testing, for example, FDA would look to, does a test do what it purports to do, does it identify a particular precursor of a disease, does it identify a disease that is taking place.

Where we look at health outcomes in our definition of reasonable and necessary, does knowing that particular fact in any way alter the health outcomes or the care management of that patient.

DR. MC CABE: So if post-market data were collected on a test that helped with understanding outcomes and clinical utility for that test, would that be helpful in your decision-making?

MS. SHERIDAN: I think it certainly would be helpful, and would be part of the evidence that we consider as part of our making our coverage determinations.

DR. MC CABE: One of the things that we have as an option and part of our charge is to make recommendations to the Secretary regarding changes. You mentioned that there are no national coverage policies for specific genetic tests, and these are done by the contractor advisory committees.

What is the makeup of those advisory committees, and is there any regulation as to the makeup of those advisory committees? Are those done purely on a voluntary basis by individuals within those regions?

MS. SHERIDAN: We have general instructions to our contractors that give broad instructions about how they comprise their local advisory committees. We

don't give any specific requirements about which particular organizations need to be represented. They do need to have a broad representation of the local specialty societies and members of the health care industry that have an interest in that.

DR. MC CABE: Similarly on the MCAC, is there a makeup prescribed for the MCAC?

MS. SHERIDAN: Our MCACs are chartered advisory committees. At this point in time we have six medical specialty panels. We have one for diagnostic services, we have one for medical-surgical services, one for DME, one for imaging, one for devices -- I'm blanking on the sixth one, I don't think it has met yet. But the actual composition are people who have expertise in that particular panel, but it is not defined as particular organizations.

DR. MC CABE: It is obvious where I am going with this. If genetic testing is going to be increasing as we anticipate that it will, then it would seem that it would be appropriate to have the expertise on both the CACs and the MCACs to review those genetic tests.

Then finally --

DR. KANG: Dr. McCabe, I'm sorry, we actually do go through a process to select people to sit on the panels, coming up this year. We would be glad to entertain geneticists who are interested in being on the panel. We go through a whole clearance process.

The only thing I should say there is, presumably if a genetics issue came for a decision, then obviously we would want those people. So why don't I make sure I know who the best person is, but when we go through our next round of selecting

members for the panel, I should try to figure out who I should contact. We would be anxious to get nominations.

DR. MC CABE: We have had a lot of contacts with people. We have an extensive email list reaching out into the community, both of providers and individuals who have much more personal concerns about genetic disease from their own perspective.

So I would think -- I'm speaking for Sarah, but it would seem appropriate to use that extensive list to try and identify individuals who would be interested in working with you.

Finally, my last question. Do you know whether there are any geneticists currently on any of the CACs or MCAC?

MS. SHERIDAN: There are not any on the MCAC at this point in time. I don't know about the composition of each of the individual carriers. They don't report their members to us.

DR. MC CABE: Then my final question is pharmacogenomics, and whether you had -- you were talking about a number of different kinds of testing. I'll ask broadly to the panel whether you have begun to think about pharmacogenomics and testing for genetics where it is not a genetic disease, but it is a genetic trait that may influence the utilization of drugs, and what the side effects of those medications might be.

So I'll just open that up broadly to the panel.

MS. SHERIDAN: From the Medicare standpoint, we have not nationally embarked on a formal investigation of that. However, we have been in dialogue with some of our contractors, particularly in the area of oncology and predictive values with

that, and helping them work through local policies and decisions on that.

So we have some background information. It is a potential for a future national coverage decision, but at this time, we have not.

DR. TUCKSON: Well, in that case I guess we will have to be real brief.

I'm glad that Ed McCabe reminded us to think about the charter. That is what I want to do for a minute. I really appreciate the intensive background you have given us. I want you to look at it from the other end of the telescope, particularly you Ms. Sheridan. What is not working? We have to report back to the Secretary. Are you getting complaints, any, from physicians out there who are frustrated by determinations to not cover, to not reimburse, in this area? Are we getting complaints from the public in any way? What is broken here, and what kinds of things, if any, do you want to bring our attention to as we look to trying to solve problems?

So this is your opportunity to tell us, what other things do you need to be able to do better in this area for the American people? Jeff has been very good about continuing to tell us about legislation. I know you can't recommend legislation, but what do you need? Or is everything perfect in Mudville?

MS. SHERIDAN: The two issues related to genetic testing that we have been most involved with nationally has been the drug issue related to oncology and also related to HIV, resistance testing, and phenotyping for indications of changing pharmacological treatments. So that is where most of our interest has been, and the questions and complaints have been coming in to us in the past couple of years related to genetic testing.

They have related to a number of issues, from the home brew and FDA

issues and assuring quality of care there. Apparently, the predominant manufacturer or producer of a lot of the HIV phenotyping does a lot of its work on European soil, and so the Medicare requirements related to foreign services have come into play there, and have been questionable.

We have surprisingly not gotten a lot of comments with regard to the preventive services aspect of this. I guess that relates largely to the Medicare patient population being aged and disabled, as opposed to children and younger families.

DR. TUCKSON: Thank you for that. Let me just ask a last question. Dr. Witt, I appreciated your comment on noting the value in the genetic information for case management and personal decision-making and others.

Given the variability in the Medicaid program, I am real worried now about this constant education that we have gotten today, as to the inability to easily affect the Medicaid program, 50 different states, 50 different ways of doing it. For us on the access committee, this is going to be a bear to make recommendations.

Do you have evidence that we can get from you offline that would help to make a compelling case as we perhaps try to influence the Secretary in how she communicates to the states about the value and importance of having good and most aggressive coverage for genetic services? Can you share with us any experiential basis you have to be able to make the case that there is value in this information, that it makes a difference?

DR. WITT: Yes. I think certainly that is available. My own personal experience, if you take Huntington's disease predictive testing as a paradigm, I have done that for 11 years now, and have worked with a lot of patients who have gone through that

testing, where they weren't asymptomatic when they started, and remain so post testing, but certainly gained all kinds of positive results from having that.

I think anyone who is involved in that kind of testing will test the same thing. There have been some formal studies looking at that kind of data over the course of the last 10 years or so, where more and more of that testing has been done, looking at outcomes and the personal effect on the individual patient.

So that is there, and I think that is the kind of thing you are asking about, do your people really have benefits, and they do, mental health, for one.

So I think there is data out there that can support that, but it is a different quality data than you get in terms of recurrence of angina and things like that. That is part of the point of all this, that we are dealing with a little bit of a different animal, and one has to be willing to accept a different kind of outcome and different kind of data in some ways.

DR. PENCHASZADEH: I have a couple of general concerns I would like to get a response from the panel. On the one hand is this question that we are seeing this diversity of health coverage policies for genetics. We heard and appreciate your presentations, but in a way they show that there are a number of variables in determining coverage policies.

I have a specific question for the representatives of the for-profit sector here. The very existence of your companies depend on making a profit, that is why you are in business. So what I would like to know is, what is your responsibility to your investors, in determining your coverage policies, beyond all the technicalities that we are discussing here?

The other major issue is that of discrimination, based on genetic characteristics. We heard very little here. I was looking at your charter, what we told you to present to this commission was not one of the major issues. However it was touched upon, was mentioned that there was a specific provision at Kaiser Permanente, the right to refuse membership because of high risk. The later presenter also mentioned something about possible -- the fact that people with symptoms might be affected in their policies, at least in the individual policies, not in the group policies.

As a practicing clinical geneticist, I have to admit I haven't witnessed specific discrimination events, but I have constantly to deal with the patients to have the fear of discrimination by their insurances, a fear that led them to either withhold going for genetic tests or deciding to pay out of pocket simply because of the fear of discrimination.

So I would like you to address how you would see this question of presence of family history or issues that may lead someone to become classified in a high-risk situation, affect the policy and hence the access to the service.

So that is two issues. The first one addressed specifically to the for-profit companies, and the second which is more general.

DR. BOMBARD: I'll start, alphabetically. Complex question, Victor, I'll do my best. Perhaps by way of answering one of Reed's questions first about frustration, I tried to point out in my briefing that there is the frustration in trying to establish coverage guidelines when there is not unanimity of opinion by the relevant professional organizations that payers of all ilk look to for what is the right thing to do. Medicare is different from ACMG is different from ASCO is different from ACOG, and that is a frustration for us.

I think that the Secretary, your panel and the Secretary by extension could be useful in bringing together representatives from those organizations to help present a uniform approach to consistency of coverage for genetic issues, and some guidance.

I think that gets to the issue that you asked about regarding discrimination and fear of discrimination. I'm a physician. I have been in academic medicine for 20 years, and it wasn't until the last decade that there was any push at all at the medical school level, at the provider level, at the employer level, about genetics. There are a lot of us out there that need to learn more about genetics. By having a uniform -- whether it is federally-based or maybe based from the AMA -- a uniform approach to what is genetics, what can it do for you, why not be afraid of it, how can it help you. Now and in the future, I think we can get to a lot of that.

I was in practice, as you know, at Einstein. We had a cancer counseling clinic, and there were a number of women who came for counseling that would have been ideal candidates for BRCA testing who were unwilling to undergo the testing for fear of dissemination. That is one of the reasons that I took the position that I did, is to try to develop a program where we could at least partially address that fear, provide genetic testing that is available between the provider and the lab and the insurer is not involved.

As the fruits of the human genome initiative are cultivated, though, genetics is going to play a greater and greater role in further defining preventive disease. This kind of gets to your first question about for-profit and the purpose of the company. We are a health care company, and we exist to improve health care and health outcomes for our employers.

It is my personal belief, and I believe I have the support of the company or

I wouldn't be here, that genetics affords an opportunity to get to true prevention. I am an ob-gyn, all I have is a hammer, so everything looks like a nail. Breast cancer; the standard of practice now is to offer screening mammography annually, beginning at age 40, every three years beginning at age 50, whatever the standard is that the individuals use. But the goal is to identify a tumor that is present early, and then treat it aggressively once it is detected. Breast self examination, ovarian cancer, annual pelvic exams, looking for a mass and then acting aggressively.

Genetics for the first time allows us to identify those women that are at greatest risk and truly improve outcomes through the implementation and coverage of medical and surgical therapies. I think we have to look at long-term strategies that will improve the long-term health of the population. That is our focus as a health plan. We have a number of disease management programs that get that. Employers appreciate that, because employers want their employees to be working and healthy. I think keeping your customers and your constituency happy is the key to success in business. I can't speak for the stock price lately, I hope that will be a long-term successful strategy for us.

Does that answer your complex question? Is that complex enough an answer?

DR. PENCHASZADEH: I appreciate that.

MR. BYKERK: Maybe I could comment next. One might presume that we are a for-profit company; we are actually a mutual insurance company. That doesn't say we aren't interested in making a profit, because if we continue to make losses we won't be in business very long. So obviously we have to make a profit to continue to be a viable entity.

On the other hand, you really get down to the issue of cost. I'm going to focus on individual insurance here, because most of the other people are looking at group insurance. Individual insurance is purchased by an individual based on their own motivation, and typically paying one hundred percent of their premium themselves.

In that environment, anything we add to our policy, anything that we enhance our benefits by is going to increase cost. A typical individual policy holder is on the books for between two and three years. They are going from one place to another in most cases.

Now, the actual curve of the length of duration of a lifetime is dipped in the middle, because people stay for either a very short period of time, or they stay for a long period of time. But the typical average policy is about two to three years when it terminates.

Adding genetic testing, particularly in a stage where its high cost disputes over what is recommended, et cetera, is probably, just to be straight honest, not going to do much for an individual policy's viability as a product. It is going to increase the cost, it is going to -- if you look at it and say, but it could improve the health of the individual, that's fine; is the individual willing to pay that. Is it going to reduce the eventual payments by the policy because it prevents some kind of disease 10 or 20 years out? Yes, it may do that, but not for that policy. It will be for somebody else.

I think that is one of the issues you have to wrestle with in working with the whole genetics issue relative to insurance. You are spending money now to save money and to promote better health much later on. Who is going to get the benefit? There is this benefit relationship kind of thing.

With respect to fear, I would again encourage you to get hold of the paper by Mark Hall, who did an extensive review and focused on health insurance. There is tremendous fear out there by people, and we have to figure out some way to fix that, as my colleague next to me here is trying to do, and I would agree with that.

There is tremendous fear out in the marketplace by individuals thinking they are going to get their health insurance policy canceled or so forth if they have high claims. For the most part, you can't do that. We don't do that as an industry, we can't do that. We are not like the auto insurance business. We don't terminate people that have three wrecks.

We deal with people as a pool. We can get out of the business, but we don't pick on individuals. Yet, the common man out there or common woman out there thinks that that happens, in spite of the fact that there is no evidence.

I don't know how we are going to deal with that. It is obviously something we have to deal with, but there is that factor that we are going to have to work through.

MS. DAVIDSON: Following up on Victor's question and the last speaker's comment, I have a question related to the reporting and disclosure polices about genetic test results. What I would be interested in is, when is a genetic test -- the result of course is related to the family or the individual, but then who else might the results be passed on to? Have companies developed specific policies or procedures? Do those results go back to not only the insurance company, but to the payer, the employer, in the case of a group insurance plan?

Anybody can jump in.

MR. BYKERK: In our case, as far as we're concerned, that is information

between the individual and their physician. It is not information that would come to us, even if we paid for it. The request obviously to have it done and reimbursed would come through us, but the results of the tests would not come to us.

MS. DAVIDSON: Is that a stated policy, or that is a procedure in general for all test results, genetic and non-genetic?

MR. BYKERK: Generally, yes. In treatment situations where you are paying a claim for accident or sickness kind of situation, obviously there has to be some evidence that treatment was provided and so on. But in the case of a test like this, the actual results of the test would not be disclosed to us.

MS. DAVIDSON: Others on the panel? Is that the industry standard?

DR. VILLAGRA: I would echo the same policy. There are confidentiality policies on the release of any information of this sort that would be applicable here.

The decision regarding what use is given to the information, particularly the results of a genetic test, will rest on the treating physician and their patient if there are implications for family members. But there are explicit policies that this sort of information is not disclosed. In fact, we don't receive the results of genetic tests to begin with.

But more broadly, this type of information is not released to anybody.

DR. LEWIS: We have about five or 10 more minutes, and I was just wanting to make sure that everyone who had --

MS. DAVIDSON: Anyway, I have another question.

DR. LEWIS: Can we give everyone a chance to ask one first, please?

DR. KHOURY: I'll try to be brief. Actually, many of my questions have

been answered, but I would like to thank the panel for being here. This was highly educational for me, and I'm sure for the rest of us.

I'd like to make a few sort of public health oriented remarks, followed by a simple question to the panel. It seems to me what is driving a lot of what we do is a split desire between protecting the public from premature or inappropriate use of genetic tests as they develop from research to application, and many of those tests fall in that category; they are prematurely or inappropriately used.

However, we want to make sure that when there are tests that have proven benefits, there are the issues of access and equity and so on. So it is a delicate balance, and you guys are thrown with this complexity, how to make differentiations between things like clinical validity and clinical utility, terms that we take for granted, although I have heard many people equate clinical validity with clinical utility, just because the value of information is valuable. When you inform people about the penetrance or positive predictive value, some view it as value itself. Given the state of complexity of this field, what worries me is this sort of heterogeneity of what this population is right now. Tremendous technology is moving quickly and we are stuck with the inability to uniformly apply it.

Take for example the newborn screening example, which is only in my mind a small fraction of many things to come in genetics. A person born in state X will have a different panel for screening than a baby born in state Y. There are state differences there. I'm sure if you take an adult who goes to Kaiser or whatever, they will have different sets of criteria.

So in the absence of this generalized either FDA regulation or

recommendations from task forces or professional organizations, each company does their own technology assessments or evaluations. I heard David -- you don't do formal technology assessments, but you have an individually-based decision-making. You said 90 percent of the time, you agree among yourselves. Maybe another company -- I heard 50 percent of the requests are turned down.

So my question to all of you is, do any of these internal deliberations -- can become in the public domain for us to find out? If we give you a few case scenarios, would you be able to come back and tell us whether this instance is covered or not, or is proprietary information? In other words, 800 tests today are on the market. I won't give you all 800, but maybe a few of the. Would that be a possible exercise to do, or is this too proprietary of information?

That is a question for all of you, for-profit or non-profit.

DR. VILLAGRA: I think part of the issue is that benefit design is often up to the employer. One of the challenges for us is to -- and the first challenge, is to try and reach some sort of scientific consensus on what is the appropriate use of a particular test.

The second challenge is that there are variations in the way benefits are designed, and we are bound by differences in benefit language. So that creates something that is outside of the scientific realm.

The third is the factor that you mentioned for, for example, HMOs that are subject to state legislation introduces yet another non-scientific if you want, or remotely more scientific source of variation. So that is where the individual crafting of a particular policy becomes very much a part of the individual company.

But in truth, the scientific assembly of clinical practice guidelines uses

pretty much the same sources.

DR. KHOURY: So would you be willing to share the results of those deliberations from that? If we give you a hypothetical scenario based on the science, -- see, my worry is that there is heterogeneity in the interpretation of scientific evidence. Just like in newborn screening and many other areas of medicine -- and I don't want to take too much time, Judy, but I would like to hear some --

DR. LEWIS: I hear your point, and I think it is something we can follow up on in the access working group. We have one more person on the list, and I'll end with Barbara's question.

DR. KOENIG: I'll be very brief, since I know everyone is anxious to get up. One comment which I would like you to perhaps consider. We heard a lot on our panel about the promise of molecular medicine as a new frontier in preventing disease. But what I am hearing, what I heard on the panel, was incredible structural barriers to implementing the promise of this new technology.

So I guess I am feeling sort of sobered about the ultimate possibilities at this point in time, without really significant restructuring of the system. So that is a general question.

A more specific question is, the other thing that I heard in terms of specific policies across the board with the exception perhaps of Kaiser is the linking of clinical utility with the actual coverage of say a genetic test. So my concern is, are there policies on the books at this point, so that if there are no proven interventions associated with a test, that it would on that basis not be covered.

The issue there is, is this simply the right to have the information or the

right to know, or the psychological benefit of knowing, not considered something that is of clinical utility?

MS. SHERIDAN: With regard to your first question, I think that at least from the Medicare program standpoint, that there are not insurmountable burdens to Medicare coverage, as long as the science is there. If you are hearing beliefs about the value of a particular test as opposed to science demonstrates it, then perhaps there are some problems. But if there is science that supports the value of a test with regard to improving clinical health outcomes, the Medicare program is very quick to take that science into account and to develop a national coverage policy from that science.

DR. KOENIG: I thought preventive services were prohibited just by definition. Am I misunderstanding something?

MS. SHERIDAN: I'm talking about -- I'm not talking about the preventive services. As long as they are within the scope of the benefit of the Medicare program, is the caveat.

DR. LEWIS: At this point, given the time, I'm going to say thank you to all of our panelists for being here, and also I want to thank Suzanne Goodwin in her work, in working with people to help to arrange this.

DR. MC CABE: Thank you, Judy, and I want to thank everyone on the panel. It has been a most informative morning, and we really appreciate your willingness to come and share your experiences with us.

I think one of the things that I heard was Dr. Bombard making a very specific comment and recommendation. That is, to consider whether we should recommend to the Secretary the development of a group to help determine a consensus

and bring some rationale between the statements of different groups. So I would hope that your committee would consider that recommendation in your deliberations.

Again, thank you very much to everyone. We will take a break.

DR. KANG: I'm hearing two other recommendations that the access committee ought to consider here, because quite frankly we are dancing around the issue here.

The issue quite frankly is, what is a health insurance benefit. That is really what you are wrestling with here. In general, what you have heard most of the health insurers saying is, we've got to improve outcomes. What you are saying is, is information itself a health insurance benefit. No one has made that -- society at large has not made that decision.

The other question is, is primary screening a health insurance benefit or a public health mandate, if you're going to do broad based population screening. Those are the two fundamental questions that you are wrestling with here, and the access committee really needs to sort through what it wants to say there.

Until you get society at large to say information by itself is a health insurance benefit, you are going to be dancing around this thing.

DR. MC CABE: Thank you very much for your help with additional focus. I'm sure the access group will take those comments under consideration as well.

We will reconvene at 10:50.

(Brief recess.)

DR. MC CABE: We will hear from Dr. Schoonmacher, director of medical reimbursement and government affairs from VISIS. I would ask each of the

public commenters to limit your remarks to five minutes, please.

I want to thank Michelle for inviting the SACGT to participate in a symposium that you organized at the recent American Society of Human Genetics in Philadelphia. We appreciate your giving us that venue to present our preliminary thoughts to the public. Thank you, Michelle.

DR. SCHOONMACHER: Thank you, Dr. McCabe. Thank you for the opportunity to address the Committee. I'll speak to points that are discussed in more detail in my written statement.

Many private and public groups act independently to evaluate new technologies. Many times, these groups reach different conclusions regarding the value of a new test. While the FDA determines safety and effectiveness, they do not evaluate medical necessity in the greater context of total patient management as the payers do.

As a result of the disconnect between FDA evaluations and those performed by payers or other groups, FDA approval no longer guarantees that coverage will be available for a new test.

Coverage decision-making involves determining the medical necessity of a test or service to diagnose or treat illnesses or injury, or to improve the health condition of a patient. Coverage criteria are often elusive. As Judy alluded to, what is the definition of medical necessity? How do you prove that something is not experimental? It becomes difficult for manufacturers then to design clinical trials that answer these pertinent concerns.

From earlier testimony and from my dissertation research that was submitted earlier, it seems that insurance companies cover two separate factors in

determining coverage. They are shown in Figures One and Two in my written comments.

Of primary concern are medical and economic factors that are associated with the new tests. Once these characteristics are established, it appears that factors relating to the environment in which testing is performed can influence the coverage decision.

We have heard a lot about coverage this morning from our payer representatives. So I'm going to talk to you a little bit about the effect of payment.

Even if a test is covered, the level of payment impacts the utilization. Poor payment can have the same effect as a non-coverage decision. Where clinical experience is needed for determining coverage and payment, it is difficult to get that clinical experience without having adequate payment. Some payers establish flat fee reimbursement by CPT code, sometimes using Medicare fee-set schedules as a starting point. Others reimburse on a percent of bill charges or a capitated basis. Often, the payment amount depends on the type of insurer, the location where services are performed, and the level of benefit that the patient has purchased.

Although it would make sense for the payment system to reflect the costs of testing, the role of cost analysis has yet to be defined in a systematic way. Under Medicare, the laboratory testing is paid for according to a national clinical laboratory fee schedule. A lab fee schedule was created in 1985 at 60 percent of the prevailing rates of each of the independent carriers. All adjustments to payment levels are based on the original 1985 calculations.

In 1997, the Balanced Budget Act froze fees and lowered the national

payment limit to 74 percent of the median reimbursement established by each carrier. Notice that it is the median reimbursement level and not the provider charge. Carriers can be given complete discretion to establish their own pricing methodology at the local level in a process called gap filling.

Appendix A in my written comments gives examples of Medicare's rate setting methodologies for a micro deletion test using FISH. A typical lab charge for a micro deletion test would be about $150 to $200.

In 1998, inadequate CPT codes led to a reimbursement of about $80 for the micro deletion assay. In 1999, new codes became available and were subject to gap filling. As a result, some payments varied markedly between geographic region.

When the year 2000 fee schedule was established, carriers who had paid more in 1999 under gap filling methodologies had to reduce their payments to the national limit for the year 2000. Carriers who were paying below the national limit in 1999 did not raise their payment level to the year 2000 fee schedule amount.

Rates are often below the costs of performing the tests, especially for low volume testing situations. CPT codes do not distinguish between different types of medical tests, where payment is the same regardless of whether the test is an in vitro diagnostic, an assay developed using analyte specific reagents, or a home brew test, despite the different levels of regulation, quality control, and clinical utility that are documented.

One solution is to establish a collaborative and coordinated partnership between the developers, regulatory agencies, payers, professional societies, and patient groups as the SACGT has done to explore the issues. Ideally, the determination of

appropriate and practical data elements should be agreed upon and collected during the course of an existing or future planned clinical evaluation, rather than trying to collect them after the test is made generally available.

Where FDA review is required, payers can be allowed to participate in the review, avoiding the redundant presentation of data that may lead to different conclusions being reached by different agencies.

I realize that they have different mandates, and they have to answer different questions, safety and effectiveness versus reasonable and necessary, but the processes that they go through to arrive at those conclusions are generally the same. They involve literature reviews, talking to experts, consultation, and testimony. By taking some of that redundancy out of the system, we believe that we can shorten the process of review and also add value to making the technology determination, by having the pertinent players sit down in the beginning and define what elements need to be collected before somebody starts a clinical trial, to help get the information that will be needed by all the people downstream, or if longer outcomes are needed, at least plan for a mechanism to be able to collect that, once the FDA has made their determination of approval.

Professional societies can play a larger role in documenting the non-experimental status where a test or technology has received regulatory approval, has been validated, and should be eligible for reimbursement.

Finally, on another note, I'd like to take a minute to explain why we believe the use of social risk is a criterion for classifying genetic tests as problematic.

First, I sincerely hope that our written comment didn't leave you with the

impression that we take social issues lightly. Genetic testing highlights a basic problem in our health care system, and that is that there are no universal protections from the misuse of health status information.

Regulation of genetic tests as medical devices needs to focus on the safety, effectiveness, and medical risk. Once approved, the test becomes a tool that provides health information. It is what people then do with that information that defines the social risk.

Because social risk is such a difficult concept to implement, we can think of a social risk for almost every medical test. We do not think that delaying the availability of a test or raising the level of scrutiny just for genetic tests on the basis of potential social risk will be an adequate solution to the problem. Rather, the enforcement element should focus on the people that misuse the information.

We believe the most effective solution will be to enact federal legislation that makes the practices that we are all concerned about illegal. Only when protection of health status information is a basic civil right will we begin to alleviate the fear and concern that surrounds medical testing situations for all patients, not just those undergoing genetic testing.

Thank you.

DR. MC CABE: Thank you. Just a comment regarding your last point about the fundamental issues and needing to deal with those. The Secretary's Advisory Committee did send a letter to Secretary Shalala in the spring strongly supporting the need for the legislation to ban genetic discrimination, to take what had been done by the President in his executive order and extend it to all Americans. So we support you

strongly in that.

Are there questions for Dr. Schoonmacher? Yes, Barbara.

DR. KOENIG: Just one follow up on the social -- I think we have talked before about your concern about the social risk category. I think based on this testimony, I am beginning to understand what your concerns are, which is good.

But I want to ask you, if this is true, you seem to be defining social risk as exclusively discrimination. I think maybe one of the reasons we are not communicating about this is because we are looking at issues of potential social harm that go way beyond just the issue of genetic discrimination, which perhaps could be ameliorated with enactment of some kind of protection policies.

DR. MC CABE: Do you want to give some examples, Barbara?

DR. KOENIG: Well, for example, the issue that we are thinking about, in terms of tests that might be targeted to people of different ancestries, and how that would need to be considered, how labeling for example of those kinds of tests might need a special level of scrutiny.

DR. SCHOONMACHER: I think it has to do with our perception of ethnicity. When people go in for a health assessment, the physician looks at you, and there are certain physical characteristics that will help him decide what kind of conditions you are at risk for. Are you obese, are you underweight, are you redheaded and fair skinned, are you at higher risk for skin cancer, et cetera.

As much as these physical characteristics are going to segregate the population, genetic characteristics are also going to segregate in some populations. We need to start thinking about them not as an opportunity to hold it against somebody else,

but as an opportunity to help them with whatever health risks are apparent in their group.

DR. MC CABE: Any other questions? Thank you very much. Our second public comment and our last, unless someone else is in the audience who wishes to let one of the staff or Sarah know, our next speaker is Miss Agnes Masne, an RN representing the Oncology Nursing Society.

MS. MASNE: It is a pleasure to be here to represent the Oncology Nursing Society. ONS is a national organization of more than 28,000 registered nurses and other health care professionals dedicated to the excellence in patient care, teaching, research, and administration in the field of oncology.

It is within the scope of cancer nursing practice that oncology nurses with specialized training and skills provide cancer genetic counseling and are adding to the evolving body of knowledge within cancer genetics. We thank the Committee today for the opportunity to speak and to offer commentary regarding reimbursement for genetic testing services. You have already gathered some very important information this morning regarding reimbursement practices, and we commend you for your thoughtful and timely consideration of this matter.

Our first area of commentary is focused on reimbursement for cancer predisposition testing that has been gleaned from a variety of oncology nurses working in the field. As you have already heard this morning, there are an increasing number of insurance companies that are providing either partial or complete coverage for cancer predisposition testing. However, a significant number of individuals who could derive clinical benefit from the testing are not covered. Medicare and Medicaid do not pay for the predisposition testing for cancer, so this limits access to those who have private group

insurance or the means to pay for testing. Lower income and minority populations often do not have access to genetic testing.

Since the testing is costly, limited insurance coverage or partial coverage that Dr. Schoonmacher had just mentioned for the testing is often an additional barrier for those seeking genetic information to guide their decisions regarding cancer risk reduction. In some cases and in some states, nurses have reported that individuals who are already affected with cancer are not covered for cancer predisposition testing, assuming that the testing will provide no further benefit to them. Hence, there are national inconsistencies for covering testing.

The findings from a growing number of carriers of cancer predisposition genes are providing data about clinical outcomes and the clinical utility that was mentioned earlier, that will provide vital information for decision-making regarding cancer risk reduction, chemo prevention, screening and/or prophylactic surgery.

With this background then, we would propose the following recommendations. In order to provide greater access for low income and minority populations, Medicare and Medicaid coverage for cancer predisposition testing and of course the broader area of prevention in general must be considered.

Individuals affected with cancer are essential to the genetic testing process. First, testing an affected family member provides the most cost effective and relevant information to other family members. We recommend that guidelines for insurance coverage for cancer predisposition testing include testing affected family members where this information will benefit both the affected and unaffected members.

Since genetic testing is expensive and inherited cancer predisposition

accounts for only a small portion of all cancers, we recommend that criteria for insurance pre-authorization of genetic testing be established, and this criteria should be modeled on peer reviewed data that is emerging from verified carrier data, genetic consortia, and working groups that identify family history and independent risk factors for predicting the presence of mutations. So we would concur with that recommendation that was made earlier to the Committee about developing a special group to come up with these types of guidelines.

I have provided some examples, Aetna U.S. Healthcare in the Northeast region, does have a pre-authorization that is based on research data, as well as the American Society of Clinical Oncology has proposed a standard of 10 percent or greater probability of being a carrier, to consider genetic testing. Again, all the probabilities are based on mutation prevalence data.

Our second area of commentary is related to the reimbursement of nurses who provide counseling for cancer predisposition testing. The Oncology Nursing Society has had since 1997 an established position statement on the role of oncology nurses in cancer genetic counseling. ONS has recognized cancer testing and risk assessment counseling within the scope of oncology nursing practice.

ONS has established that the advanced practice nurse, that is, those with master's preparation and specialized training in cancer genetics, are ideally suited for practice in counseling and education regarding cancer predisposition testing. Most comprehensive cancer centers providing testing include oncology nurses as part of their team. Advanced practice nurses who provide these services have generally received additional and specialized training in specifics related to hereditary cancer genetics,

psychosocial counseling, informed consent, and medical management of the high-risk individuals.

ONS also has a special interest group composed of nurses who currently important these services. Many are recognized nationally for their knowledge and expertise.

We therefore recommend that insurance carriers recognize nurses as competent providers of the services for cancer genetic counseling, and we also recommend that this Committee propose the inclusion of nurses for medical provider recognition for reimbursement of genetic counseling services related to cancer predisposition testing.

The Oncology Nursing Society wishes to continue this dialogue with the Secretary's Advisory Committee as it develops its recommendations to the Secretary, and we look forward to future work that will ensure that cancer predisposition genetic testing and other testing as well is accessible to those who need it, and that the individuals who receive this testing are supported with the highest quality of counseling and professionalism.

Thank you.

DR. MC CABE: Thank you, Ms. Masne. Are there any questions or comments for Ms. Masne? If not, then thank you very much. Are there any other comments from the public?

We have received written comments from the International Society of Nurses in Genetics (ISONG), and also from Ms. Deborah Lockner-Doyle, state coordinator for genetic services, Washington State Department of Health on behalf of the

National Society of Genetic Counselors. A copy of Ms. Doyle's comments are in the green folder, and the others, the comments from ISONG, were handed out around the table today.

If there are no other comments from the public, then what I propose now is that we revisit where we ended the day yesterday, and look at the model as it was developing. Muin and Wylie are going to present what they worked out last evening, and see where we have come with this model, and if we can at least begin to have some discussion at this point, because by the end of the day we will have completed this discussion and be prepared to forward our addendum to -- we have already forwarded one addendum -- forward the modified addendum to Dr. Satcher, and then on to the Secretary.

So Wylie, thank you, and Muin for working on this with your colleagues last evening.

Discussion of Test Classification Methodology

DR. KHOURY: Under the influence of a good dinner.

DR. BURKE: The starting off point for our discussion was this model that we were looking at yesterday, and some of the questions that we were getting into as we got down to the end of the model, and how you figure out what is predictive and diagnostic, and what about all those three criteria that had somehow gotten lost. There was a third issue, which was, should prenatal diagnosis receive special consideration.

So we are going to show you a flow sheet that addresses all three of those questions, and does things a little bit differently as a result. But I think it leads to some questions that needs to be resolved.

At the top, it looks pretty much the same. Analytic validity, yes, no, if no, test is rejected. The next question is, is the test being proposed for population screening, yes, no. If yes, it goes to level two. Then, is it rare or not, and we acknowledge that there is a question of definition to be resolved about what is rare, but the answer to that is yes or no, if yes, it goes now to level R, meaning a particular level of scrutiny related to rare diseases. If no, we now have a step that has been put in, but I think probably needs to be discussed because I know it is controversial, that is, a yes/no on whether or not it is prenatal. So this is an option to at this point pull out prenatal for scrutiny level two, so that is optional.

In terms of the option, one could just omit that step. So that is a step that could be there or not, depending on how our discussion goes about prenatal. Whether or not you omit the prenatal step or keep it, the next item after this, the change here is to drop diagnostic and predictive. The rationale for that is lots of disagreement around the table about what represents diagnostic, what represents predictive, plus the issues that Pat has particularly identified about how much that would shunt everything into a diagnostic, and to maybe game the system.

But that pushes us back to the checklist. It is the same checklist you have seen, except that we tried to define predictive value a little bit, and that is also open for discussion.

But the checklist is three items. Once you have gotten past the population screening, past the rare and past the prenatal, if you keep it, you've got three checklist questions about the test: is there an effective intervention -- and I think what we are saying is, is there an effective intervention for test positive people -- is there a high

positive predictive value, which we find arbitrarily for the moment as equal to or greater than 95 percent, and is the test free of social risks.

If the answer is yes to all of those, you would go to level one. If the answer is no to any, you would go to level two.

DR. MC CABE: So there are several places that we need to have some clarification and discussion. Muin, do you want to make any comments before we move on?

DR. KHOURY: What this boils down to on a practical level, if you apply it today -- and I have been thinking about what we did in terms of looking at the 800 tests, once you get past the population screening, which initially most of these tests were not introduced for population screening, you enter the domain of rare versus common. Most of the common stuff would fall into level two right now, because there are very few of those where you have effective interventions or positive predictive values more than 95 percent.

So another simplified way to think about the existing scheme right now, translated into reality, is rare versus common. However, we have set the stage for future applications of genetics, especially in the domain of pharmacogenomics, in the domains of uses, the social aspects of prenatal diagnosis, et cetera, and doing away with this arbitrary distinction between predictive versus diagnostic, which I think people have problems with.

The other comment I wanted to say is the definition of rare disease. That is something we need to resolve, but I don't like the definition of the Office of Rare Diseases, the 200,000 people in the country that exist because there is no denominator. If

the U.S. is suddenly one billion people instead of 300 million, 200,000 is meaningless. This is a prevalence-based estimate rather than incidence-based estimate.

I found out from my office, the Canadians use things like one in 20,000 in Canada as a cutoff for rare versus common, but I don't know if this is incidence or prevalence-based. So it is a bit more complicated than that.

Then of course the definitions of social risks have to be discussed. So if this Committee can come up with very simple guidelines to help this review process -- and right now, if I have to apply this, it really boils down to rare versus common, because most common stuff will fall into level two and most rare stuff will fall in level one.

Did I mistake something, Wylie?

DR. DOYLE: No. I think the other thing to say is that most genetic tests that we know today are going to fall into the rare category. That depends a little bit on where we draw the threshold, but the genetic tests, particularly the ones that we are really concerned about, that represent a small number of families for whom we want to get tests out quickly, those are going to fall into the rare category.

DR. MC CABE: Discussion on this?

MR. HILLBACK: I said I wasn't going to be first, but I guess I am.

Now I am concerned that we are making the decision based on what I would call non-scientific evidence, rare versus not rare, than where we started to try to be, which was that we were going to try to be a little scientific about this. Things like free of social issues or social risks, I don't know which test is going to meet that criteria, free of social risks. My card-carrying anthropologist, which you haven't stripped from me yet, although Dr. Koenig is trying -- so I am not sure that this is helped, in that sense, in that

we are going to push an awful lot of things to level two, or are we just going to take them out just because they are rare, which may solve some short-term problems, but I don't think for the long haul sets us up as having created a workable system.

DR. MC CABE: Do you have suggestions, Elliot?

MR. HILLBACK: No, because I couldn't cope yesterday, either.

DR. BURKE: I'd like to make two comments about that. One is, just because they are rare we pull them out, I'm not sure that would be a fair description of this scheme, because we haven't defined what is in level R.

I think we heard conversations that level R should be an adequate level to assure safety of the test, et cetera. So I think maybe all that does is, it recognizes that the way you look at the evidence is influenced by the prevalence of the disease.

So if you accept that as an extenuating argument there -- I agree completely with you that free of social risk is problematic, because I don't know how to define it. We have it here because it was part of the list. My personal opinion is that there is a concept behind that, but that until we can operationalize it, it is probably going to be very hard to put it into a scheme.

So with that comment in mind, how would you feel about a checklist that used intervention and positive predictive value as thresholds for level of scrutiny? Just putting aside the definition of social risk for the moment because it is problematic. Again, we are not saying tests don't get passed; we're just saying we would look a little closer if predictive value is lower and there is no intervention.

MR. HILLBACK: If you're asking me, I'm not enough of an expert to go back and say, is 95 percent a good indicator. What you tried to do I think was to try to

find an indicator that was more scientific than predictive versus diagnostic. Maybe this is the right level or the wrong level, and that could certainly be worked on. If that solves that problem a little bit, I don't know, I'm at a loss. I haven't figured out how to do this.

MS. BOLDT: If we take out the free of social risks, we should leave the prenatal box in, because I think that is a big step. I think we have heard from the disability groups too, how we have to be very careful with that component.

The other thing, I think the positive predictive value is a little high. I'm just throwing that out, in terms of the 95 percent.

But Mike Watson made a good point yesterday in terms of looking at individual diseases, but we also need to look at individual mutations. I wonder if this is the spot to talk about that, because what I am thinking about the CF, we get to the positive predictive value, where are we going to put that for the different ethnicities? So I think that is going to be a problem for that.

The last thing is, in terms of prenatal, could we include that to be PGD? I am assuming we are, but it would make it more explicit. But that would also be pre-implantation genetic diagnosis, and not just prenatal.

DR. BURKE: I just want to comment that we could keep prenatal tests separate, or we could offer that as an explicit, concrete, very measurable evidence of potential social risk.

There are two different ways to slice that. One would be to keep social risk in, and define it very concretely, one definition being test offered for use in prenatal testing. I agree with you; I assume pre-implantation genetic testing.

I think what I was hearing was, the idea of using predictive value as

threshold is reasonable, and that is separate from what the actual number should be, which is perfectly reasonable.

DR. CHARACHE: I am very concerned that we include if not the wording social risk, something that makes it clear that this is a special triage based on the fact that it is a genetic test.

I think this group has got to recognize the precedent setting which would be very difficult for the FDA if we don't make it clear that this is a unique set of diseases.

This is also the basis for which CLIA put forth new policies and a new discipline category of genetic testing, with more stringent guidelines proposed than for other types of diseases. It was because it affected kindreds and families, and did have some pejorative or perceived pejorative aspects to the population designations which result in given patterns.

So I would like to figure some wording there that we could come up with a recommendation for how it would include maybe even social risks for heritable diseases in excess of those of other types of disorders, or something, that we could figure out how to define, that makes it different from other tests that identify serious heart disease or something else.

DR. PENCHASZADEH: I would like to echo some of Francis' comments yesterday. We have done a lot of work until now on this flow chart, and we should at least keep some of the main concepts that we have agreed upon.

I just think that we should try to clarify more the flow chart. I think we did have discussions yesterday related to test volume, which was in the last version, and I think there is a consensus that test volume is not something that is practical to put in the

flow chart, for reasons that we already analyzed.

But if you take the question of test volume on the one hand out, the only real difference is that we are doing away with the distinction between diagnostic and predictive. That is probably also a conceptual framework. That is good, because predictive is something that is an added thing that we should probably discuss even further today.

DR. BURKE: And we have just heard that we could incorporate that into social risk.

DR. PENCHASZADEH: Yes, but actually if you look at our previous flow chart, we did agree that significant potential -- and not only for social risk, we mentioned for medical or social risks -- was an item that was going to draw any test to our highest scrutiny.

And we addressed already the issue of whether or not there is an effective intervention. So the only thing we are adding here now is, in lieu of diagnostic versus predictive, we are actually putting a level of predictive value, because we were talking about low predictive value.

DR. BURKE: Right, it was implicit.

DR. PENCHASZADEH: Yes. What we are saying is that we really want a test to have a high positive predictive value. Otherwise you will have to go to a higher scrutiny.

So I don't see any major change, other than clarifying the question of test volume, including then the question of rare diseases. I agree we have to find a better definition for rare diseases. That will indeed accomplish what our goal is, which is to

make sure that diseases that are infrequent, or mutations that are infrequent, that should not be a barrier for developing and having access to a test.

Now, the question of prenatal diagnosis. Every single test will be applicable to prenatal diagnosis eventually. Once you can determine a genetic constitution, the technology is here today to be applicable to prenatal diagnosis or precondition diagnosis and so on.

Yesterday I was voicing a concern that prenatal diagnosis should have some social considerations of some sort, but on the other hand, it is true that practically all tests will be applicable to prenatal diagnosis. So I don't have an answer for that.

I still think prenatal diagnosis is a very important social event or social issue to consider, but those are primarily at the level of policy; what is something that is amenable or ethically appropriate to be subject to prenatal diagnosis, and for what purpose, interrupting a pregnancy, or eventually these things may change with the advent of prenatal therapies and so on and so forth. So as I speak, I would leave prenatal diagnosis out.

DR. LEWIS: I just want to speak very, very strongly to eliminating the category of prenatal diagnosis. I really think it has an opportunity of treating a special population adversely just on the basis of being child-bearing, the reality or the potential. I have real problems with that. We have spent a lot of time over the last twenty years making sure that pregnant women don’t have to receive special treatment and have the same rights and privileges as everybody else. That is very important to me because I think that whether a woman is pregnant or not pregnant, she has the same rights of autonomy to information and I think that getting information is not necessarily bad to a

decision of whether or not to terminate the pregnancy. I think those are two very separate pieces. I think if we confuse them, we are making the same mistake that we have seen in a lot of places. I think they are two very, very separate issues.

In terms of keeping in the social risk, we could look at pregnant women as a population that may be subject to stigmatization or discrimination. So by keeping the social risk category, we may be able to deal with that. But I would be very, very concerned about keeping that as a category. It is something I feel very strongly about.

DR. KANG: This is a place where I am sorry I missed all the previous meetings, because I am trying to struggle here.

Let me make sure I understand this. This is based on the test's analytical validity, you are trying to triage, quote, into a kind of regulatory oversight?

DR. BURKE: I think the analytic validity is just acknowledging a test doesn't even get into the pathway unless it has analytical validity, so that is a small part of it. That is the first thing that you would assess in a test, does it have analytical validity. If the answer to that is no, you're done, you don't go down the path.

DR. KANG: What is happening here is then, analytical validity, by separating your populations based on prior probabilities, --

DR. BURKE: No, it is a claim about the test. Is the test being offered for use as a population screening tool. Have I got that terminology right, Steve? It is a claim.

DR. KANG: It's a claim, I see.

DR. MC CABE: In the parlance of FDA.

DR. KANG: I think I'd got this now. At the third level here, what is level

one? Is that level one oversight versus level two? Level one is less regulations? Is that what I'm hearing?

DR. BURKE: That is more streamlined and quicker.

DR. KANG: It is interesting. What you heard this morning from the payers' perspective, they are interested in covering those tests that could lead to effective interventions. I think we would be comforted if there was sufficient regulatory oversight. So I would almost --

DR. MC CABE: This would not be in absence of regulatory oversight, but given that there are 800 tests, it would be a way of streamlining the evaluation of the vast majority of those tests. So that is the discussion that has gone before.

DR. KANG: I see. I'm not sure what streamlining means.

DR. MC CABE: It would still be reviewed.

DR. KANG: It would still be reviewed, but you would put it up at the top of the list.

DR. MC CABE: What we had talked about yesterday also is the labeling and the data that one would collect as part of the labeling, that would be true for all tests.

DR. KANG: I think I'll get together and try to --

DR. MC CABE: Why don't you huddle over lunch with some folks? Joann.

DR. BOUGHMAN: I'd like to make two or three observations here. One of the major changes here is the inversion of the population screening question and rare versus common, or the term we used before with -- I can't remember what the term was. Muin said a couple of times that in fact, it boils down to rare versus common.

I am having trouble with the definition of population. I believe the definition of population screening might be different when applied to rare versus common. And given that we have a kick out here suggested into a special level R review, I would like for people just to think for a moment about re-inverting to putting rare first into the level R that would ask the questions about population screening, slightly differently, or have different expectations versus on the common side.

I don't think it changes the intent here, and I think it addresses the issue that the interpretation of population screening might vary slightly.

Another question that I would like a little bit of discussion on is the concept of effective intervention and just how broadly we are addressing that issue with regard to not only prescriptive therapeutic interventions, but lifestyle changes or even the potential effective use of information received from genetic testing. I think we have dodged that bullet so far.

I don't expect necessarily a straightforward answer to those, but I wanted to --

DR. KHOURY: I guess the simple answer to why we inverted this was the fact that you might have rare conditions that are introduced to be screened for in all newborns, things like galactosemia or MCAD. From a public health angle, I'd like to see those scrutinized heavily to know whether there are interventions, regardless of how rare the condition, because we are subjecting all newborns to that test.

Now, the definition of population in my mind is -- that is one type of population, meaning everybody, all newborns. The other would be sub-segments of the population, like targeting Ashkenazi Jews for certain tests. You can see the list that fell

out from our analysis of the 800 tests and the GeneTest database.

So from the public health angle, this was a way to make sure that the ones that are going to be used for population-based screening, be it carrier or newborn or all 14-year-olds for whatever, these are segments of the population regardless of the rarity of the condition.

The second point I wanted to say, if you do that step at the beginning, you realize that most of these tests were not initially introduced for population-based testing. No one would do that, even the MCAD. So industry will have a way to go to the second step, and then it becomes a question of rare versus common, assuming that most tests would not be introduced initially for population-based testing. Then the cutoff would be rare versus common.

When you go to the common, that box in the middle essentially is the initial review of -- look at these three parameters there, the clinical validity, clinical utility, and ethical and social data. So somebody will do an initial review of those and determine somehow whether this will be shifted into the level two area requiring people to collect more data more vigorously. You have to define the difference between level one and level two.

So for a common disease, after an initial review of clinical validity, clinical utility, and social data, then if the answer is no problems there, then it becomes a more or less routine oversight. But for most of them, they will fall into level two. That is the reality right now.

So that is why I was not being cynical, but I was saying right now, it boils down to rare versus common. If we want to make sure that the rare tests are not stifled in

the progression from research to practice, then we create a special category for them. Otherwise we have the same model for everyone. Look at the analytical data first, if it is okay, move on; then look at the clinical validity, clinical utility, and the social data, and that is what it boils down to. It is very consistent with the framework we have put forward.

DR. BURKE: And also, in terms of the fact that we have interventions other than a specific medical intervention for a test positive person might have value. I obviously agree with that completely, but it seems to me, the point of the checklist, or at least our interpretation of the point of the checklist, was -- what we are really saying is, is it a slam dunk. So, this is an accurate test, there is an obvious helpful intervention, there are no obvious stigmatizing or discrimination-engendering kinds of issues.

If it is that, if documentation can come in to that effect, it ought to have a very streamlined process. If the documentation is more complicated, if it involves a more complicated discussion about what kind of benefits might come out of having the information, which carries with it maybe some more complex pre-test counseling, for example, then it makes sense to me that it has a higher level of scrutiny.

But I should say, I am assuming that there are two things that are major concomitants of the higher level of scrutiny. One is being very careful about test labeling. So it seems to me, I want tests to come in for the higher level of scrutiny if I want to make sure there is a good review of how the test is going to be labeled. The other is the post market data collection. So if we are uncertain about what kind of interventions might be associated or whether they are really helpful or not, it seems like that is a test where you want to earmark some specific suggestions about post-market data collection.

DR. MC CABE: Judy and Michele, and then I'm going to come back to call the question on several of these issues, so that we can at least know what we have decided this morning. So, Judy.

DR. LEWIS: One of the things that would help me a little bit is, we are talking about different levels of scrutiny, some of which being streamlined and some of which -- I don't know what the opposite of streamlined is, but more detailed, shall we say. To have the sense of what the levels will entail would be a little helpful.

I think we are proposing theoretical categories, but it is real hard to have a handle on what the difference between those categories are. My assumption is that the rare category will mean that you will need less data, but that doesn't necessarily mean that the data will be any less robust because you've got a smaller number, but in terms of looking at research, one would expect that you would have smaller data when you are dealing with small samples.

So my question is, it would help me a little bit if I had a sense of what the different levels meant. I think slam dunk is one thing, but it gets a little fuzzy. I think even after we propose the model, once we start looking at what the various levels are, we're going to come back to the same discussion.

DR. PURYEAR: My question is, I am worried about some of the stuff that gets thrown off in population screening that has actually already been shown to be effective, but we have just sort of left it there.

DR. MC CABE: This is for new tests. In our recommendations that become public today, we recommended that any test with which there was experience would have a different --

DR. PURYEAR: Who defines that experience, that level of experience?

DR. MC CABE: That it has been utilized in the public, it is already out there. So we are talking about new tests. So newborn screening tests that have been utilized are already out there, and they would undergo a different review. We recommended that that be done by a consortium of professional groups.

DR. PURYEAR: So that would include reviewing then all the tandem mass spectrometry tests?

DR. MC CABE: Yes, those are out there and have been utilized in a clinical setting. What we will get to then is the line between research and clinical.

DR. KOENIG: I'm sorry, I didn't realize that you were about the close the question. I just want to speak very quickly to one issue about taking away diagnostic versus predictive. I have a concern that -- would that mean that anything that is diagnostic of a condition which has no interventions would automatically go into category two? And is that something that we want --

DR. BURKE: If it was past the rare threshold. Not if it was a rare condition. If it was rare, it would go to level R.

DR. KOENIG: I have some concerns about that, again putting too many things in category two and not meeting that goal of trying to create a streamlined system.

Also, I think the diagnostic genetic tests are quite different, do require a different level of scrutiny.

DR. BURKE: How do you define diagnostic?

DR. KOENIG: It just seems to me if you are diagnosing somebody who is already -- it is the issue that we have talked about, the sense, the intuition that predictive

is more complicated if there are no interventions.

DR. BURKE: Right. I'm not asking a facetious question. How you define diagnostic becomes very complicated.

DR. KOENIG: I recognize that, but it also seemed to me that another way of dealing with that might be with the labeling issue. I totally understand the motivation of taking it out so that there is not a way of gaming the system. But we haven't ever addressed the issue of whether there might be alternative ways of dealing with that problem, for example, via some kind of enhanced labeling, which would basically say that this particular test has not been approved for predictive use.

DR. BURKE: Just to clarify, I understand your concern. I actually fiddled with some alternatives, I think coming from the same concern.

I think we need to put an example to the point you are making. The example is, what if we had a test like Huntington's, but it was common? Huntington's can't serve as the example, because it is going to go in the rare.

I think that is the first answer to what you are raising, is that the genetic tests that we can imagine that might fit into this quandary really do for the most part fall into rare. We are talking about high penetrance diagnostic, where we have confidence that we can diagnose.

But I think it may be an empiric question, that is, how many tests really fall into this checklist situation.

DR. KOENIG: Then just two last things very briefly. I think we cannot punt the prenatal issue. I think we have to find some way of addressing it, and I think it may require some more discussion. But I think we can't simply ignore the fact that this is

a very serious question.

I would feel more comfortable if there was a way in our flow chart to get level R tests that -- there might be some that do require level two scrutiny, and that there would be an out at the other end, so that even though they are rare, there may be some that could be bumped up. That was in our previous model of rare diseases under one, and that would make me more comfortable.

DR. MC CABE: Elliott, and then I do want to frame the discussion a little bit.

MR. HILLBACK: You asked me a while ago, what would I do. If we need to get somewhere today, I think Judy made a good point. We haven't heard Steve weigh in and say this is what level one is going to be like, what level two is going to be like. We have challenged them to do that, and I'm sure that they are working on. I know they are working on it; it is going to take some time.

I would prefer to use a combination of what is there and what we had yesterday. I would leave the first three things that are there. I have some concerns with each of them, but it is better than anything I can come up with.

But I would go back to predictive and diagnostic below the big black stripe there, because I think tests are arrive on the scene that have the nature of being predictive are going to absolutely need a higher level. This is where Francis has been all along, this is where we got started on the discussion 18 months ago. Things that arrive on the scene that are fundamentally diagnostic -- I think we all want to push to level one.

I think in the end, we are going to find that this model is a good starting point. Someone else said this awhile ago, maybe it was Judy, as we get into real life and

try and look at the scheme that the people come up with, and also understand how we are using this whole thing to manage clinical practice, not just manage laboratories, because that in the end is what we are really charged with, that we are going to have to say the model doesn't quite work, and we've got to fine tune it.

To get one on paper and to get it to go forward, I am much more comfortable with the predictive versus diagnostic as the third or fourth box down. But I like the way we have changed the top end on what is up there now.

DR. MC CABE: Thank you. Let me tell you what I would suggest. That is, I think that we have always considered this a work in progress. It needs to be tried out. We need to then fine tune it.

I would suggest that our goal today be to come up with something that can then be tried out, that Muin can model, using the approach that he used before. It might be helpful to the FDA as they are considering what these levels of scrutiny are. It would give their group something to mull over.

So my goal is not to come up with something that we are going to inscribe forever by the end of today, but something that people could try out, that perhaps the Lab Forum could take a look at again in the interval between now and the next meeting in February. Maybe that will give people a little more comfort and less a feeling of finality, if we take that approach.

But we do need to help people with the modeling. And certainly you can then vary these thresholds, but you can try them out. I would suggest that you try two different cutoffs, and they are the ones that we talked about yesterday. One would be a prevalence of one in 2000 where we have prevalence data, or an incidence of one in

10,000, since for many of these we have better incidence data than we have prevalence data.

The one in 10,000 -- I know that it was mentioned that Canada uses a one in 20,000, but that means that we include diseases like PKU, which I think many of us would consider a relatively rare disease in that grouping. So I would just argue, at least as a place to start with the modeling, that we use those two figures, and try them out and see how they work in your model, Muin.

The issue about social risks. I think that if you say free of social risks, taking Elliott's comments, that because of fear of stigmatization and discrimination, there is none of these tests -- part of why we are doing this is because of the fear of social risks that are inherent in genetic testing.

So I would argue that we should specify social risks well above those inherent in genetic testing, because if we say free of social risks, if this went through any IRB in the land, you would never find free of social risks, in any group that would come up come up with this.

So we have to set a level of social risks that is above that inherent in all of these. I don't know if that would be acceptable to the group, but I am throwing these out for discussion later this afternoon.

We need to discuss the PND, and whether we are going to eliminate that or not. What I have heard around the table is that it is still very mixed. The argument is that prenatal diagnosis could be done for any disease, so that doesn't really discriminate for any of these diseases, but there are significant concerns about the prenatal applications. Whether that becomes again an issue of labeling and experience with the

test and security with the test, we can discuss later.

Then the issue of predictive versus diagnostic, Elliot has spoken to going back to those terms more generally. I guess I for one, speaking as a member of the Committee and not as the chair now, was pleased that we had put some quantitation on those and the positive predictive value, whether it is 95 percent or 90 percent. I would think that it would be in the modeling, but I think that that would be helpful in the modeling to have a number, rather than just diagnostic versus predictive.

One of the things that if you have genetic heterogeneity, how do you account for that? How do you deal with that in terms of the positive predictive value? Again, it would be good to have a number, and see what that did to the threshold. But I'll give Elliott the opportunity to rebut that.

MR. HILLBACK: The question is positive predictive value of which population. As you get into the one question, if you look at all women, you don't have anything close to that. If you look at a certain subgroup, you do. The subgroup is where we would say, this is a diagnostic test for this subgroup, it is not diagnostic for the majority. So if that takes you into level two automatically, you are now changing the time lines and the costs and everything else of doing that test.

So I see where you're going. I did want to say, I think your other comment about prenatal, if you use the significantly elevated above baseline social risks, which I don't know how to define, you may pick up that subset of prenatal tests that have a very high perceived risk without generalizing that all prenatal tests necessarily have that risk.

DR. MC CABE: What I would also ask, and this I don't think we are going to resolve today, because these definitions are hard to hammer out, but I think I

would ask Wylie's group to look at some of these definitions in the interval between now and February, that we look at what is a population, because that is a very fundamental definition. Are we talking about the entire population, are we talking about -- how would you utilize that term in here, and then the other definitions as we went along as well.

With that, this was really just to summarize what I think we have talked about. This afternoon at the end of the day, we have two tasks. We have to finalize this, but again, not as final as I think we entered these two days. We need to get it to a point where people can begin to model it. Secondly, we need to hammer out that patent letter, and then we need to look at our priorities for each of the working groups.

So with that, we will reconvene at one o'clock. Thank you.

(The meeting was recessed for lunch.)

AFTERNOON SESSION

DR. MC CABE: We want to go to the discussion of the informed consent IRB team's progress. Dr. Barbara Koenig has organized a presentation from a leading scholar of the ethical and social implications of genetic information. I am going to turn to Dr, Koenig to introduce Dr. Nancy Press. We hope that Dr. Press will also be able to stay with us for Dr. Koenig's presentation of her report on the working group.

Presentation on Informed Consent in Clinical and Research Settings

DR. KOENIG: Thanks. I should say that the idea of doing a presentation to educate the Committee about some of the complexities and issues in genetic testing and informed consent for genetic testing was the result of deliberations of our entire subgroup.

That said, I am very pleased to introduce Dr. Nancy Press, who is a friend as well as a colleague. She is a fellow medical anthropologist. So there was some bias in the selection, I will say that. She is an associate professor in the Department of Public Health and Preventive Medicine at the Oregon Health Science University, where she is also assistant director of the Center for Ethics at OHSU. She is trained as a medical anthropologist and her work has focused on the ethical and social implications of genetic information, plus a wide array of conditions, including CF. She is currently working on hemochromatosis, and I think of most interest to this Committee, she was the only social science member of the first NIH-DOE-ELSI working group's Task Force of Genetic Testing. So she has a lot of history in terms of the issues we are deliberating today.

I should say that we have worked together for quite a long time. We first

began working together after the BRCA-1 gene was originally mapped, to try to think ahead to what the ethical implications of the eventual cloning of the gene would be. So it has been awhile and that was interesting. So Nancy, we look forward to hearing your talk.

DR. PRESS: I don't think that it is possible to come to conclusions about informed consent about genetic information until one has a grasp of the limitations of the problems involved in informed consent, in general. So I am going to start out talking about that. I think of informed consent as having three interconnected parts. One is providing information which is there in order to aid in making a decision which is then documented by an informed consent form. It is interesting to me that the second of these, making a decision, which is really the whole point of the enterprise, is essentially ignored in the literature on informed consent or is rather assumed to be transparent and not problematic. Even for bioethicists, for whom the autonomy of that decision is paramount, the process of decision-making is something of a black box. But saying that now is perhaps beginning at the end, so I would like therefore to start by describing what I think is the bioethicist's ideal view of an informed consent encounter, and then move on the present a somewhat revised model which focuses on the barriers to actual decision-making.

I think if you were to schematize the ideal informed consent encounter for a bioethicist it would look something like that. The sheer decision that results down here are seen as the outcome of the patient subject and clinician researcher and something that goes on within the informed consent encounter. As represented here, the patient has a

certain educational and cognitive level and the clinician is attuned to it and is able to communicate in a language that the patient can comprehend. The patient subject asks questions and gets answers and this requires the patient's willingness to ask questions and the clinician's skills in creating an environment which elicits those questions, as well as having the appropriate knowledge to answer them. In concert, these things constitute a shared decision-making process. In this model the joint aspect of that process is shown by the double arrow.

The first point to make about the schema is that, based on empirical data, there is little doubt that informed consent conversations rarely achieve this ideal, either in clinical care or in research settings. The largest amount of empirical research has been done on the first part of informed consent, which is how successfully is information communicated. What studies have consistently shown is that often little information is successfully imparted to patients or to research participants and even less of that information is remembered after a little time.

I actually put together some references--it is not exhaustive, maybe 20 or 30 references--and they are circulated to the committee. I am going to touch on some of the studies that I are in there if you want to look a little bit more. What I am going to give you are some standard kinds of things.

Byrne interviewed a hundred patients within five days post-surgery and found that almost half were unaware of the exact nature of the surgical procedure and one-quarter did not know what organ had been operated on. This is, of course, with a consent form signed. In another prospective study of surgical patients, the majority could not explain any of the terms that appeared on the consent form. That goes on. Reasons

cited for this lack of effective communication transfer begin with the finding that many patients don't read the consent form. In another study of surgical consent, Lavelle Jones, et al found that 70 percent of patients admitted to not reading the consent form before signing it.

There have been a couple of researchers who are unconcerned about this. For example, McCormick and his colleagues concludes that the willingness to consent for procedures that people don't understand "implies there is an element of trust involved in the process of giving consent." These authors believe that this aspect of the doctor-patient relationship should be legally respected. That is, when the patient signs without knowing what they are signing, that should be legally fine. But the majority of researchers were disturbed in their research to find how poorly informed consent actually was taking place.

The next question is, why don't patients understand? Why don't patients, rather, read consent forms? One of the major reasons is summed up inadvertently by the same McCormick, who wasn't worried about the fact that consent had taken place. McCormick supports the contention that such incomprehension about what is going on, while not problematic, is un-fixable. What I would think is probably the funniest line in an abstract that I have read, McCormick complains that the majority of patients in the study, even after receiving information, "remained unsure of the meaning of such simple terms as fracture reduction and internal fixation."

So turning the slide on its head, the major reason cited in the empirical literature on the problem of informed consent is the high level of language that is found in them. Study after study found the language level far too high for the majority of patients

or research participants. This is true even when forms are purportedly written at a high school reading level or below. Jubelirer suggests that one problem with the use of readability scales, which are now built into just about every computer program, is that individuals often don't read at the grade level they have actually attained in school. His survey showed that 30 percent of patients with a tenth grade reading level, in terms of where they had gotten to in school, could not read at that level. It is therefore not surprising that numerous studies find that level of education is the most positive predictor of comprehension on a consent form.

So why is it difficult to write a comprehensible consent form? Certainly anyone who has tried to write any sort of educational material knows that making complex concepts easy is a daunting task. However, I was particularly struck by the conclusion of a study by White et al in which they investigated the readability of a variety of research consent forms submitted to institutional review boards by medical researchers. Their conclusion was, quote, designing a consent form to meet all of the federal requirements while maintaining a level of reading comprehension suitable for the general population is a very difficult task for investigators, close quote and understatement.

So the most noteworthy aspect of all this research however may still be how thoroughly it focuses on the consent form. So the first thing we know is that the consent form is not working very well. But why is there so much emphasis on the form. This document has become so important and yet it is not working as an informing device. Perhaps we should think a little bit about what its purpose is.

Certainly it is a legal document that has not become mired in liability

concerns and regulatory language. But at its most bare it is a form that documents that information has been provided and understood and that this information has been used to aid in the making of a decision about a service that has been offered. The consent form is the least important aspect of all of this. It is merely supposed to be a confirmation of what went before. In fact a scholar named Lidz had created a useful distinction that is often cited between an event form of consent, which focuses on the signing of the form, and a process model which stresses an ongoing educational give and take between the physician and the patient.

Clearly the bioethical ideal of informed consent is talking about the need for this sort of process model of informed consent and clearly this ideal is not being achieved. But let's assume for the moment, just of this conversation, that we have somehow magically figured out how to institute this process, this ideal which focuses largely on getting information across to a patient in a culturally and educationally appropriate and sensitive manner. If that were to happen, would all the problems be solved? I still don't think so. I think there would still be a problem because, as an anthropologist, I believe that this bioethicist's ideal model is still an inadequate model of informed consent.

The informed consent encounter as shown in the first schematic is a bounded interaction that goes on between two parties within a clinical encounter. In reality, however, some of the most important barriers to effective informed consent occur well before the clinician researcher or patient participant enters the consultation room. These barriers come from the world outside the clinical encounter. So this figure is a

representation of some of the most important of the structural factors that shape the informed consent encounter before people go into that room.

The respect that is felt for medical authority in this culture is certainly not an unknown phenomenon, but it receives surprisingly little attention in the informed consent literature. This respect for medical authority comes from many sources. For example, patient vulnerability at the time of the medical consultation; belief in science as the source of solutions to most problems; a sort of secret, sacred code aspect of the language of medicine, et cetera.

However, all of these elements are exacerbated when there is also class distinction between the physician and the patient and this is often the case since physicians are high ranking members of our culture. Such a class difference, which is highly correlated with educational differences, not only makes it more difficult for the patient to understand consent documents, it also makes it much more difficult for precisely those patients who most need to ask questions, because they are having trouble reading stuff, to feel free enough to trouble the physician or the researcher by asking those kinds of questions.

Now from the point of view of the physician there is simply often insufficient regard for these issues. However, even the most sensitive clinician, one who is quite aware of these issues, is basically left on her own to devise ways around the problem. All the bioethicists' models really say that the clinician should be nice, respectful, sensitive, open, encouraging. Yet in examining this more inclusive schema, it is easy to see that this is not enough. There are sensitive egalitarian doctors and there are cold, hierarchical doctors, but neither strategy can undo what exists before either the

patient or the physician walks into the consult room. The perception of the legitimacy or the necessity of the test or research endeavor, which is the next item here, is itself shaped by a broader belief in the value of information. In contemporary U.S. culture, knowing is part of an assumed package with doing. Knowing is a kind of doing and knowing, it is thought, will inevitably lead to doing. Thus the assumption that diagnosis will always lead to improved health outcome, that finding a gene will quickly lead to finding a cure. According to physician and bioethicist Eric Cassell, this attitude is particularly marked when information is provided by medical technology, which Cassell says American biomedicine is addicted to.

Here in this case, with the value of information, it is actually the similarities rather than the contrasts between patients and providers that make true decision-making difficult. Then there are issues further down the schema that are not quite in parallel for the practitioner and the lay person. The patient subjects may have different degrees of difficulty in finding or expressing their views, depending on the medical context. Serious illness makes a person feel very vulnerable. And the very trust in science and sharing of the decision may be the last thing a person wants to do, probably because the need to make a decision logically implies there is not one right answer. People, at a time like that, are often looking for the one right answer.

The patient or subject also comes to these decisions not as an individual but as part of a group. Some of this is currently acknowledged--for example, the need to be culturally sensitive. But there are other things that are not so easy to deal with. For example, a pregnant woman of a certain age has a lot of peer pressure and peer expectation that there are certain kinds of tests she is going to undergo, for example,

amniocentesis. On the clinician researcher side there are also pragmatic considerations that some patients may suspect but which are nevertheless largely invisible to them. They happen offstage, outside the room. These include time constraints, productivity demands, and liability concerns for the clinicians and a variety of career issues for the researcher--for example, recruitment goals.

Also a physician or researcher may have difficulty fully engaging in an informed consent discussion if he or she is not aware of personal biases in favor or against certain procedures or things it is easy to hide these personal views from the patient. Finally, as opposed to the ideal picture of informed consent in the first picture I showed, in which the arrow went in two directions, in this case the arrow in unidirectional. This indicates the tendency that I think these effects have to act on the patient subjects more than the other way around.

So do I think there are any answers for these problems? Well, social scientists are always being accused of being their own version of the dismal science. All problems and no solutions. So I am going to suggest a couple of things that I think would help.

Number one, since the consent form seems to be the tail wagging the dog of informed consent, rather than blaming lawyers, which I think it is easy to do in this case, why not simply let it remain what it has become--a legal document--and separate true informed consent from it? If the consent forms have to remain so long and complex as to be largely unreadable, it might help to create a second simpler form which is meant to document patient comprehension of just the points that are considered key, not from a legal point of view but from the point of view of what you were trying to give somebody

information about. It has often been said that people cannot really, in a learning session, grasp more than three to five points anyway, this might be one way to do it. I am going to talk a little bit later about a project that I was involved in to implement recommendations for cystic fibrosis screening. But this is the last page--it doesn't look exactly like this in the brochure--this is the last page of an educational brochure about cystic fibrosis. The page that is right next to it, over here, is actually blank except for some lines and it says it is a place to jot down questions you might have after reading the brochure, that you did not completely understand.

These are the things we felt were the most crucial. I will go back to some of them later. I think they are relevant to the idea of prenatal testing. The first one says, I understand the decision to be tested for CF carrier status is completely mine. I realize it is a personal decision, not medically required, and then it goes on to a variety of things, including number 5, which we really kind of had to fight ACOG for, but there it is. I understand that if the baby has inherited a changed CF gene from each parent, the only way to avoid the birth of a child with CF is by terminating the pregnancy. One signs accepting or declining. We tried to keep the language clear and simple. There may well have to be another consent form that covers the fact that you might scratch your cheek using a buccal swab or something like that. That is the main point. So that is number one.

Number two are the structural forces I tried to show in that diagram. All work against the ability to make a real choice, a real decision in the doctor's office--the respect for medical authority, the setting, the feeling of vulnerability. Therefore, the doctor's office may be a good place to impart information, but it is not necessarily the

ideal place for a patient to make a free and informed decision. Nor is a researcher's office necessarily a good place to make a decision about participating in research. Another possibility is to remove the consent process from the office. Again, in the CF brochure, we are suggesting that patients, prospective test consumers, take it home, talk about it at home and then bring it back, mail it back, whatever. This is very different from the way I saw informed consent done for maternal serum alpha fetal protein testing in California where there was definitely a procedural bias to give the person some information, give them a minute to look at the brochure, or hand them the brochure, and get them to sign off and give consent right away.

Number three, I think is important and a little more dicey. I think there needs to be a conversation about whether informed consent is a right or a responsibility. Certainly informed consent literature has overwhelmingly focused on the idea of informed consent as a right. But there are a few authors, and I do include myself here, who have considered at least whether or not it is also a responsibility of the patient to make a fully informed decision. Since the literature on the failure of informed consent, some of which I summarized earlier, implies that patients may at times be eager to leave the decision-making to the physician, I think this is a real issue. I think it is particularly germane to genetics, certainly for prenatal testing, but also for research projects where a person's own participation, or clinical testing, may have ramifications for their family or for some socially constructed group to which they belong. Therefore I think it is possible to be able to say that somebody has a responsibility to make a fully informed choice. It is not a very American kind of thing to say, but I just wanted to put it up here.

Finally, whenever a bioethicist, whenever I have talked to clinicians about

informed consent, about how badly it does, about what is really needed, for example, in prenatal testing, the response is always the same. It is not feasible to do what bioethicists consider the right thing to do because no one has the time to do it. I started hearing this in the early 1990s when I was talking about the dismal failure of informed consent for prenatal screening in California and that was true almost a decade ago before productivity demands were even a term currently used. It is undoubtedly worse now.

What is to be done? I would say that the state of informed consent in clinical care is never going to get better unless there is a way to make it important. One way to make it important has already been tried -- making it a legal requirement for certain procedures. However, I don't think this has led anyplace particularly good. It has led to all the emphasis being on getting legal consent rather than informing someone and helping them make a decision.

So what is to be done? I think we are in a capitalist society and I would say if you want to make something important, you have to pay for it. I think you have to use the legal obligation of getting informed consent to force the creation of some kind of CPT code structure to cover this endeavor. If there is no way to get this done as a physician service, then there might be something that could be done, and frankly could probably be done better and less coercively by nurses. Better because of the fact that patients--and I have certainly seen this with prenatal patients--actually feel freer to say to a nurse, could you go over that again, I really didn't get that. I know this is not an easy thing to make happen, but I simply believe that hand wringing over informed consent is going to continue until the carrot is added to the stick. So that is my feeling about informed consent in general.

The next question is, how does all this relate to genetics? I think the question immediately following that--what is different about genetics--a question that certainly the Task Force struggled with and I know that your group has struggled with and I am not going to try to solve that here. But my position anyway is that there is less that is different about genetics than the rest of medical care than the public discussion suggests. This is not that the risks are not real, but because I think the risk of other kinds of medical technology are underplayed. For example, there is little to say about the psychological burden of uncertain information, the possibility of feeling ill when one is not yet ill, or even the risk of insurance discrimination that you can say about genetics that you can also say about PSA testing.

So I think that is an important thing to keep in mind. But there are two aspects of genetics that are different enough in terms of their implications for and relationship to informed consent that I think they deserve special treatment. One is the implications of genetic information for families and beyond that for socially constructed groups. The other is the issue of prenatal testing. I want to spend the most time, therefore, on these two issues, but I promised Barbara Koenig that I would speak a little bit about the implications for informed consent as genetic information kind of went through the sort of soup to nuts different areas. So I am going to try to organize the second half of the talk along the lines of various stages and settings in which one finds genetic information, but concentrate most on research with families and prenatal testing.

I have come up with a categorization organization device for myself and it is on three different overheads and it starts there with research. So we are going to start over there with gene hunting. The issue of the familial nature of genetic testing is most

often discussed in the setting of the primary care practice, where one patient is seen but the information revealed has implications for family members. So basically clinical care. However, families are involved in the very beginning of genetic research in linkage studies and that has consequences for informed consent that I am not sure have been examined enough.

For example, as multiple members of a family are enrolled, participation may lead to a social redefinition or realignment of the family unit, exacerbating tensions or strengthening familial bonds. This is something that Barbara and I are very familiar with, but I am not sure it is the first thing that pops into mind with people who work in genetics is that a family defined genetically is simply one potential definition of a family, and it is not necessarily the most relevant one in terms of the families that people live in. So when you start doing linkage research and such, you are in a way imposing a particular template of the family on a social group.

This heightened sense of genetic family may become a powerful motivation for research participation. It may also increase coercion on previously uninterested family members -- the hope of older members of the family to be able to do something for younger and future generations. They also may make it difficult to keep the line between research and clinical care from blurring. All the later problems that may involve families and genetics and informed consent I think are pre-figured at this stage. I happen to have a little ethnographic data I want to present because I think it makes the point clearly.

It is from a study in which I only had a marginal involvement. I was called on to consult. The principal investigator was an epidemiologist who was interested in

getting funding for a psychosocial arm to what was an ongoing study looking at BRCA 1 and 2 mutations. I was asked to consult about how to do that. Therefore I was kind of given free access to the research project and asked to join in certain things. When the study was first funded it was viewed as non-clinical research and the PI and the funding agency had agreed that no results would be returned to participants. The informed consent form that family members signed did state this explicitly and the proposed psychosocial arm that I was asked to be involved in would include the disclosure of test results and studying the effects of that disclosure. An assumption was made that psychosocial effects would follow disclosure, rather than psychosocial effects were implicit in the research itself. At this point of the study there was no social science component and no counseling component.

I have done, I hope, I think, all the right things in terms of making changes to protect the truly innocent, but keeping the patterns more or less the same. So this is the pedigree. A, over there, and I know I am using non-standard markings, nomenclature, so the geneticists in the audience will please forgive me, but A, over there, the proband, was diagnosed with breast cancer and that is how the family got involved in the study. She quickly became a quasi-member of the research team, calling her relatives and encouraging them to part of the study and giving permission for obtaining their medical records. A talked with the investigators as to what she might say to reluctant relatives to persuade them of the importance of the research. When the family's pedigree was complete and medical records had confirmed the diagnoses, it was necessary to obtain blood from a large number of family members and it was decided that the research would go to a location convenient to the family--a kind of gene hunter method.

As you can see from the pedigree, R died of ovarian cancer at 62 after having five children, two sons and three daughters. The proband A was diagnosed when she was 37. Coincidentally, a couple of months after the family became involved in the study, A's cousin, H, over there, was also diagnosed with breast cancer. As you can see, that left K, up there, who herself had breast cancer, as the only living affected relative and one with a daughter. Both of R's sons had died in their forties. According to the family, both deaths resulted from alcoholism. That was reported by the family, and to the family this is as much a part of their genetic heritage as was the cancer. When H, over there, was diagnosed with breast cancer, it led to this shift in the relationship of the family to the researchers. Before that, A had been running the show, K then completely took over. She was extremely motivated to get the whole family involved. She was older and a little bit more central in the family. She did a lot of the phone calling. She arranged to have the event, a sort of family picnic and blood draw, at the hospital where she was known and where both she and her daughter had been treated.

On the day of the blood draw event, 40 members of the family, including spouses and even some close friends assembled and conversed. I kind of mingled with them. A frequent theme that I heard was concern about the young people in the family, suggesting that a significant motivator in participating in the research was the hope that the younger generation would be saved from what the older generation had suffered. The family also seemed very eager for help from the researchers for putting together the puzzling aspects of their particular genetic history. For example, several of them asked about G, up there, who died of ovarian cancer, and talked about the fact that she was the thinnest of the sisters, she ate the best, she did everything right, and they wanted to know

what's up? What can we do to protect ourselves if that kind of living well did not help?

Others brought up the fact that the women who had ovarian cancer were dead, while those with breast cancer were still alive, but no one woman had had both types of cancer. They wanted to know if there was a way of predicting which disease somebody would get. There was also a lot of discussion about the two alcoholic brothers, which was just, to them, a part of the whole picture. The family was eager for a confirmation of their view that it was possible that there was a gene for alcoholism which men got in the family and a gene for breast and ovarian cancer that the women got. Since they were being told they were genetically special, in one regard, this seemed like a pretty logical assumption.

When the blood draw began, the family was impatient with the length of time it was taking to get informed consent. They wanted to get to the point where they were talking to the PI and asking these questions. They had come ready to give blood and they didn't want to listen anymore to an explanation of the parameters of the study or its risks, and this was including people who had not been "consented" before because they were coming for the first time. Many mothers brought their small children up and children were not having their blood drawn, and it was hard to convince parents why not. They thought this might be helpful and they were ready to do it. What started happening was there were a couple of phlebotomists and everything was kind of slowing down. It was not going the way it was supposed to with informed consent forms quickly being read and signed. So eventually, as everybody got irritated, there was a sort of sign the form and get your blood taken and that was the end pretty much of informed consent.

The PI had a clear intention to avoid any clinical interaction with the subjects and he started to give a very general talk about BRCA 1 but it was quickly interrupted by clinical questions, most of it involving the first cousins, P and H, who wanted to know what they should do about things like prophylactic oophorectomy. In a very highly charged exchange, the proband A said she had already had her ovaries removed when her breast cancer was diagnosed and recommended this as a course of action. One of the first cousins responded saying she had periodic CA125 testing, and A shot back, But that tells you when you have the disease--why wait? Another first cousin was very upset and said, What are you saying, that we should all have our ovaries taken out? What about having children? The third cousin said A Pap smear will detect ovarian cancer, right? Nobody was quite sure about that, so they all turned to the PI who had not wanted to engage in this conversation in the first place. But he said, No, a Pap smear does not detect ovarian cancer. Basically he was asked what should we do. Tell us what we should do.

Eventually this kind of died down, but problems re-emerged for the PI when a family member asked when will you be able to tell us who you have tested has the gene and who doesn't have the gene. The PI replied apologetically that results would not be given due to lack of scientific certainty about the meaning of a positive or a negative result. He referred to the consent form which included the non-disclosure and he was met only with disappointment by family members. The PI tried again saying we only have one gene so far and a person could not have this gene but have other genes, so they can't tell anyone what it means if they don't have the gene. A, the proband, tried again, and asked Are you going to tell people if they do have that gene. If I had the gene and I have

breast cancer and my cousin does not have the gene, doesn't that mean something for her? Doesn't that mean that she is probably okay, which I though was an insightful comment. The PI merely replied that he was in the process of writing a proposal to do the psychosocial study and that would include disclosure of the test results. Test results could not be given back until the disclosure study had been funded. Whereupon, the family members gave up and asked When will that be? When will the study be funded? And the PI replied eight months to a year. However, the study section to which this study was sent did not have the same feeling and the disclosure study was never funded.

So what is the take home message from this? First, I think that is shows that research that involves families cannot ignore the social context of those families. If you ask for family member help in obtaining other research participants, you have to realize you are mobilizing a social unit. As with other social groups and social groups in general, this is not just or even, nearly, or most importantly a vulnerable social unit. It is a set of individuals who are a group and made even more a group by their participation in the research, and they have their own agendas, needs, and goals. Therefore, even without an explicit intention to do participatory research, that is what genetic research with families, de facto, is. And if one is involved in participatory research, one needs to treat the family as research collaborators. That means that the desires of the family, what they think they are getting out of the research, cannot be completely ignored, as the PI was in fact trying to do. It was not his fault. He was following a standard model, but I think this kind of tension is not unusual and right now there is no particular kind of algorithm to get out of it. Currently NIH, and I think correctly, is agnostic about what approach is best for

family recruitment, understanding that either being approached by a researcher or by another family member has a possibility of being coercive.

I think that is not the problem. I think the real problem is this mobilization of a family unit that happens by its very nature, and I think there needs to be a psychosocial kind of component to studies right from the beginning, and an explanation and an informed consent form that there is a possibility of a feeling of coercion, obligation, increased anxiety among those who do and don't choose to participate, and adverse effects on other family members. This is regardless of disclosure. But in terms of results disclosure, in general I am not certain that it is fair to refuse to return results to individuals who want them, when those results might have even a preliminary clinical significance. Or possibly no clinical significance. I think it is not a great way to treat people who have, de facto, become research collaborators, to withhold information from them. At some point during any research project something would be known. It might be a completely negative finding, and the limitations of that would have to be explained, but I think that can be explained and I think that people have to be treated with more respect for their intelligence because I think that the families who get involved in this kind of research, from what I have seen, make themselves very educated and pretty sophisticated.

Anyway, I am taking a stand for disclosure. I think all of the stuff on families leads to the next issue on the diagram, which is the fairly new field of single nucleotide polymorphism, or SNP research. There has been a lot of ELSI activity on this front, so I am not going to spend a lot of time here. Probably the most interesting is a series of meetings that have been run by the National Institute of General Medical Sciences, which has kind of found themselves with a SNP resource that is of interest and

they don't quite know what to do with it because, it is my understanding, they don't usually deal with humans. So they are a little bit at a loss. But Judy Greenberg, at NIGMS, has run these meetings and I think she would be really useful for your group to hear from. And she is great. I know that she is getting together a report from a public meeting that happened a couple of months ago and there has already been a web article about that report and I put that reference in the references.

There was also an issue of Community Genetics which was devoted pretty much, not specifically to SNP research, but to the issue of genetics in minority communities, which I also referenced. The advent of SNP research, for which the implicit unit of analysis is some sort of group, has led to the discussion of community consent as a concept. Many of the major players, in discussions about community consent, are either Native Americans or they are writing about the Native American community. Although that writing has been very interesting, and introduced this interesting idea of community consent, I really would warn against using Native Americans as a model for anything. As people who work with Native Americans will tell you, they are organized in groups that are legally able to make binding treaties. They are groups you can negotiate with as separate or private nations. This does not make them usual.

Eric Jeungst has written interestingly and forcefully on the subject of community consent in general, not specifically in the Native American community. He has an article entitled, quote, Groups as Gatekeepers to Genomic Research: Conceptually Confusing, Morally Hazardous and Practically Useless. Here is a guy who can write a title. As an anthropologist, and I don't know if you would be interested to hear Barbara's

feelings--we haven't really discussed this--but I would lean towards a similar view of Eric. From the point of view that there is more than sufficient data demonstrating significant differences between group spokesmen and kind of rank and file members of that group. Even among the Native American community, research that Wylie Burke and I did about hypothetical interests in BRCA 1 testing among urban Indians in Seattle, we found almost no effect or awareness of the rhetoric words and objections to genetics that have been very well articulated by Indian leaders. Rather urban Indians were as open to and interested in the possibility of genetic testing for breast cancer susceptibility as the rest of the group. There were some interesting differences among all the ethnic groups, but they were not anything that had to do with genetics is bad or worries about cell immortalization or any of the kinds of things that have been discussed by Indian leaders.

I can't see a situation sin which I think it would be legitimate to give the group leader the right to disallow other in that group to participate in research. My personal view, though, would be to utilize group leaders, for example, to be on advisory panels in the planning stages of research, but with the realization that these leaders are precisely there to raise issues that may not be obvious even to others within their own group. In this I think they are akin, in a way, to lobbyist or to other special interest groups. And I don't mean that in any insulting sort of way because I think that a scientist who is in a room trying to get people interested in research who has a single disease he is interested in is the same sort of lobbyist. And I think that is fine, but I think it is different than hearing the view of the whole group. However, I do agree with the concerns of many in socially constructed and highly visible minority groups that genetic information may pose serious threats to them. Thus, I think consent for individuals to participate in

genetic research that may have implications for a group should include a specific delineation of what the risks for group stigmatization and discrimination are and that is something they may want to think about in making a decision about whether or not to participate in research or whether or not to be tested.

Moving on in this whirlwind tour to this area here--research on the prevalence and penetrance of genes -- I think that largely thanks to the ELSI program, especially the Cancer Genetics Study Consortium, there are very good models for this kind of research. A paper by Gail Geller et al, which came out of the Cancer Genetics Study Consortium and was in JAMA a couple of years ago and is referenced, I think is a particularly good model when it talks about research protection that should be in place. In terms of retrospective studies on stored tissue, of which there is also a good literature and most notably the recent NBAC report. However, I think there are some issues here that have not been completely answered, although I have to admit that I have not gotten past the Executive Summary of the NBAC report, so it is possible that they answer all questions, but I just want to bring up that I am involved in a large NIH multi-center trial about the prevalence and penetrance of hereditary hemochromatosis, in which blood samples that are going to be collected from participants are going to be stored for future use. It does say on the consent form that this is the case and people can opt out of the research if they don't want to have their blood stored.

But there are a bunch of issues that have not been fully resolved in this research that is about to go into the field. There will be samples collected from 100,000 people. That is a lot of people. For example, there are issues about cell immortalization that are still being discussed, even though some Native American groups have very strong

religious objections to that idea. Frankly, although Native Americans have discussed it, I actually wonder how many non-Indians would not have perhaps some less clearly articulated discomfort with giving this gift that keeps on giving, if they really understood it.

Academic researchers have relevant questions, commercial companies who are eager for a large and diverse sample of individuals with a variety of HH mutations. And finally the flip side of that is that what is there--is there a duty to re-contact people whose samples you have if, in the future, new mutations are found. So I think that these are not issues that have been completely resolved and need to be thought about.

So this brings us to genetics and clinical care. In terms of newborn screening, Ellen Wright Clayton has done some really good work about the idea of assent rather than consent. In fact Muin and Wylie Burke have edited a book on public health in which Ellen has some stuff on that. So I am not even going to touch on that. I would like to spend the rest of my time talking about the issue of prenatal screening.

This is potentially an expanding field, of course, when we think of things like multiplex testing. It presents, as far as I am concerned, entirely different problems for informed consent. When bioethicists discuss prenatal testing, the meaning, ethics, and politics of terminating or not terminating a pregnancy, it is generally central to what they are talking about. It would be a mistake, however, to assume that the public discourse mirrors that of the scholars. In fact it may not go too far to say that certain silences in the public discourse have actually enabled the routinization and rapid growth of prenatal testing in the US. They have done this by obscuring or limiting the need for

public debate on two topics on which American are deeply conflicted, but which lie at the heart of prenatal testing. That is abortion and disability.

In research done by myself and Carol Browner on the effect of the state mandate to offer maternal serum alpha fetal protein testing to all pregnant women in California, we found that an odd confluence had occurred. Nurses were receiving considerable pressure, again these kinds of structural forces, to offer the test and document that offer from a liability perspective, and this led them to highlight certain procedural aspects of the test offer. For example, when in pregnancy it had to be done; that it was a simple blood test; that it could be scheduled right then. And this was emphasized over either a discussion of the medical purposes of the test, a real delineation of what spina bifida was, what neural defects were, or the nature of the test. The words abortion or pregnancy termination were practically never mentioned. Neither was it explained that there were no treatments available for these conditions. It was never mentioned that the decision to accept or decline the testing was a personal, moral, value-driven decision and not a medical decision.

The upshot of all of this was that we found that women who accepted the tests, and that was the vast majority of women, had actually placed AFP testing under the rubric and described it in the same terms and words as routine prenatal care. And they expected the same benefits from it, namely, enhanced knowledge, the feeling that they were being responsible parents and that they were doing the right thing, and sometimes reasonably explicitly that this test would help protect their fetus. This experience had a profound effect on me. So when I was asked to co-chair a group charged with making recommendations on that and implementing prenatal screening in cystic fibrosis, it

seemed important to craft an informed consent form that would first make explicit the purpose and nature of prenatal testing, and I showed that to you before.

So I think if multiplex testing occurs, it may be that the most important first separation--I am certainly not going to try to draw one of those flow diagrams which we have seem so many of this morning--but I think it might be important to make a separation between tests where treatment for the fetus is possible, if such happens, or where treatment of the neonate is enhanced by pre-birth diagnosis on the one hand, and on the other hand, tests where the only treatment is abortion. I think these are fundamentally different. So I think the purpose of the test should be the first and most important dividing line. Now there is already implicit in the idea the link between non-directive counseling and genetics, such a link is already there. But I think it has oddly become obscured by this difficulty of discussing abortion in America and this has led to a lot of rather confused discussion about non-directiveness. As though there was something about genetic information, per se, that required non-directiveness. But I would draw the connection between non-directiveness and genetics in a different way. This is not the simplest diagram. That is to say, that non-directive counseling is linked to genetics through prenatal testing and non-directive counseling is linked to prenatal testing through abortion. That is to say that those of us on the CF implementation committee felt that the specific content of cystic fibrosis was very important, and in fact we took a great deal of time crafting a description of CF that was not unrealistically rosy, but that did take into account the current spectrum of realities of living with CF. But we wanted to make sure that the decision process was thought through in terms of what the test could do.

We had a member of the CF working group, who is a member of the CF

Foundation. We had another person who was a pediatric pulmonologist who works almost exclusively with CF patients. So we got some real content in there. And we thought that that was important and that the decision was important. I have not had a chance to poll the committee, but it my sense that, as a group, we would object to the idea of generic consent for multiplex testing. So even though we are first saying the most important thing is to have people understand the nature of the decision and when there is a treatment and when there is not a treatment, it is also important to have some information about what the specific disease is.

I think that the feeling of the group would be if it is too complicated to offer brochures on all the things you can test for, then you are not ready to test. There is some problem there. This has to be done. We don't think you can just say to a doc, test for everything that could be out there.

We did include in the brochure language and a table that showed the prevalence of CF in various ethnic and racial populations and suggested that low disease prevalence in your group as you identified yourself might be one reason not to choose to be tested. We are leaving it therefore up the couple.

Well, I have lost all my overheads and it doesn't really matter because I am just about through. What actually the next thing would be is predictive tests done in a physician's office. I know that is of great interest to this group, but I don't think I have a whole lot to add here. If tests only get to the clinical stage when they are considered ready for use in that arena, with the types of safeguards and follow-up data collection you are all discussing, and physicians have adequate and accurate knowledge about the advantages and limitations of the test--in other words, all those easy things--then I think

you are in good shape. I am certain that you have already considered the need to form an opinion about offering tests without a physician consult. I know this gets talked about sometimes, the possibility of getting a blood sample and sending it to a biotech firm--I have heard some geneticists who worry about that, but I am not going to discuss it.
So there is just one other arena I assume considering and that is, when clinical testing is done on patients who are already diagnosed with a disease, some of the most interesting examples to me and one that Wylie Burke and I talked about a lot, is microsatellite instability testing done on colon cancer tumors. The issue here is first that the testing will be done by pathologists, not someone who is used to getting specific consent for the analysis she does. Second, there may not be a clear delineation of whose advantage this testing is for? Is it for the patient in terms of treatment or is it a cascade testing method for the family. In any case, when Geller, et al wrote that paper, there was a strong statement that I would endorse to say that informed consent needs to be gotten for genetic testing in any situation, whether it is done by pathologists or whether it is done by a primary care doc, it is the same sort of thing.

I can see Barbara looking at me. The other issues that are left have to do with confirming diagnosis, pharmacogenomics, and actually Wylie Burke has done some more thinking about that recently than I have and maybe during the group talk she could say something. So I am going to end here with a whimper rather than a bang and thank you all for your indulgence.

Report on the SACGT Informed Consent/IRB Team

DR. MC CABE: Thank you very much. Do you want to go ahead and then we will have the discussion?

DR. KOENIG: She has actually introduced a lot of the issues that we want to talk about in terms of the informed consent IRB team report very nicely. This may be the last time I ever use PowerPoint. What I am going to do is go through our report and hopefully allow most of the time for discussion, where we really want to go in setting priorities about informed consent and IRB issues.

In terms of the members, you can see on the left the members of the committee that are ad hoc members from agencies. One of the things we did, we recognized there were certain issues in this area where we would need to either coordinate with other groups or add different kinds of expertise, so we added a few other members to our working group. In particular, I spoke with Greg Koski, the new director of OHRP, and he volunteered to have someone join us. In this case they are eventually going to have a permanent genetics person, but for the moment we have had a wonderful representative, Tom Puglisi. We also wanted to involve PRIM&R, which is a group that does mostly work on IRB education, for those of you who don't know about the PRIM&R group. We had representation from the Genetic Alliance, in terms of Sharon Terry, who was here yesterday but was not able to stay today. She has been a very useful contributor. Then I also wanted to include someone who was doing research on these issues, in terms of thought through issues on IRBs and how they work and research on ethics and genetics. So we added Ben Wilfond from the Genome Institute, as well as William Freeman from the Indian Health Service.

So what were the goals of our team. Our goals, as originally stated, and we have reformulated them slightly and we are hoping to get your endorsement of those reformulations. The first was to gather some information. I will go through what we

have actually gathered. Eventually we hope to develop some informed consent templates that are well correlated with the kind of data issues that the data group is coming together in terms of what kind of information we want at particular points in the process of developing genetic tests and looking at their oversight.

We want to determine how informed consent should be implemented and documented for scrutiny levels one and two. We had a lot of discussion about that. We don't want a system in which in the research stage you are requiring one kind of informed consent and perhaps a certain kind of informed consent with signature or without a signature, and then you get to clinical practice and it totally transforms. So we thought there was a need for some kind of coordination.

Next we wanted to coordinate with other oversight activities currently going on in the federal government, in particular the current examination of the whole enterprise of human subjects protection in the US. Then we also hoped to move a little bit toward offering guidance on the whole question of social harms.

As I tried to mention, one of the things we were thinking of was the creation of some sort of a seamless system--and this may be an idealistic goal--but the way we were thinking about it is if you think about the full oversight task of how a new genetic test gets on the market, the first stage is research when it is governed by IRBs. So we really need, now that we have done our major task of making the recommendation about pre-market approval by the FDA, I think it is also appropriate to look back and consider the whole spectrum. One reason is that if we develop a system where it is extremely easy, for example, to give out results during a research phase, then the research phase may essentially become the clinical phase, and even though reimbursement may keep things

from moving into the marketplace, there still may be a lot of testing that is done without oversight or without what we would consider appropriate oversight. So it sort of identifies the kinds of phases on this slide, some of which Nancy spoke to and I would have put in our A, B1, B2, whatever, but I couldn't figure out how to draw the box. So my apologies.

So what kind of information have we gathered? Basically I have said all of these are in progress. We have looked at some model informed consent documents from different groups including NIH, and I think UCLA contributed one. We have reviewed the NIH grant portfolio and the literature looking at two things, the research on informed consent in genetics as well as trying to look at the research on IRB effectiveness and what the problems are and what really are the issues of IRB review of genetics. We have collected some information, and you have a table in your packet, about state laws requiring informed consent for genetic testing, because in some cases that is going to be a problem with harmonization. We also wanted to look at what the public concerns and expectations regarding informed consent were. In order to do that we developed a list of questions that we wanted answered and those have been posted on the Genetic Alliance list serv and information is beginning to come in. I don't have a formal summary of those yet, but that is something that we can do and I will mention just a few of the key issues that members of the Genetic Alliance have brought up.

One of our goals is coordination with existing activities. The reason for that is that we really need to focus our valuable time--our time is a scarce resource on this Committee. NBAC, the National Bioethics Advisory Committee has been engaged in a full-fledged overhaul of the human subjects or thinking through all the issues in human

subjects protection in the US including the issue of use of human biological materials and genetics is a big part of that. So what we were trying to do was identify ways in which we could move the issues forward without duplicating all that effort. So I am going to come back to that.

The key agencies or efforts we need to coordinate with are NBAC, OHRP, and in particular there is a sort of plan on the back burner or I don't know if it is on the front burner yet or not, by OHRP, the new version of OPRR, the Office of Protection of Research Risks, to revise the guidance on genetic research that they give to the IRBs that they govern. That is a very important activity and very relevant to the first phase of genetic research, when it is a local IRB, which provides governance. Finally, the other group is PRIM&R, which does a lot of efforts in IRB education, education of members, and they have genetics education, I believe, as well.

So what has NBAC done and what did we do? We had a number of conference calls and in one of those conference calls we had the executive director, Eric Meslin, really brief us fully about all of their activities and try to point out in their reports, and in particular their report, the first one mentioned, Research On Human Biological Materials, which elements of that report are most relevant to the oversight of genetic tests so that we could sort of begin and build on the work they already have done. So the three areas where they have sort of made a start, but where we could make a contribution, are the first is the consent of research samples, the second is recommendations on disclosure of research results, which was a major part of Nancy's talk and is a key issue in this whole oversight arena, and the third is the potential harm to others, or social harms. In particular, NBAC made some progress on the issues of group consent and the issues of

implications for families beyond the individual when you are talking about genetic testing. But they really feel there is a lot more work that needs to be done.

In the area of disclosure, they feel that we could make a real contribution by really specifying what level of certainty would you need to reveal research results. Nancy made a very strong statement how she thought subjects deserved results. We are going to come back to that. That is probably counter to CLIA, so it presents some problems to us. But we think that one of the things we can perhaps do is really specify that, and I will come back to that.

Then finally, in terms of major system change recommendations, the human biological materials report is done, but the report that NBAC is working on now is their report about sort of reformulating the whole enterprise. And that are very interested in correcting some of the problems that have developed. For example, the issue of informed consent moving into being seen as a legal protection for institutions as opposed to a way of informing potential research subjects in the research setting, or patients in the clinical context. So to just sort of try and emphasize process as opposed to documentation, they have a whole bunch of reforms going on that would improve the whole process. But most importantly they are going to be making or they probably already have made a recommendation about requiring that all research be governed by Federal oversight. That is an extremely important recommendation, comparable to our recommendation for FDA pre-market approval. I was just at the bioethics meeting and there was a lot of joking about how animals on the one hand and investors in the United States, on the whole, get better, more coordinated protection in the United States than do human subjects, because of the state of the system. So I think it is very important. One

of the things we might want to consider is endorsing the idea that all research deserves oversight, regardless of whether it has federal funding or not.

So in terms of the short-term tasks that we have been working on, we came up with the idea, as other groups have, of perhaps drafting a letter with some of these concrete recommendations to Secretary Shalala, and the first would be to request--and this is based on the testimony we had on the family issues--a request that OHRP's advisory committee clarify when family members are subjects. So this is basically we are asking her to do something in another one of her agencies.

Two, ask that OHRP make the update of human genetics research in the IRB Guidebook a priority. So we are basically just asking her to set some priorities -- they are working on oversight -- to make that a priority.

Then three, to recommend that NIH fund additional research on informed consent in genetic testing. And in particular, on the three areas that we think are problematic or that we are concerned about, the first being this issue of the family versus the individual, the second being the multiplex testing issues--we really don't have any idea how people are going to respond to being tested for 15 conditions. The third is how the consent requirements change across this continuum that Nancy has just demonstrated for us.

I will quickly go through some of our long-term goals. I am just about done so I am hoping there is time for discussion. First is we want to review the SACGT classification algorithm and really develop some criteria to determine which tests under scrutiny levels one and two and we just added R--that's the advantage of PowerPoint--warrant documentation as informed consent. I am not going to say more documentation.

I'll come back to it. Then we want to actually develop the templates for the informed consent documents and coordinate those again with this issue of what data, what we know and what we don't know. Finally, define responsibility for obtaining a document on consent throughout commercialization. That is an issue that we keep hearing over and over again. What can the lab do, what can the lab not do?

Next, we thought that one of the things that we could contribute is to offer some expertise to OHRP in terms of the update on the human genetics guidance for IRBs, that might be something where we can offer some assistance, assuming that both of our groups remain in existence. Finally, we might want to endorse and refine NBAC recommendations on research involving human biological materials as a way of advancing our own agenda. One of the ways we have considered doing this is to possibly commission a white paper on informed consent that would deal with all these issues. Then a final issue--and I am going to give you an outline of that possible white paper as my last slide--and also to consider issues of informed consent in genetic tests marketed directly to consumers. For example, via the Internet. Now we have sort of done these in priority areas. This probably would be a lower priority, although I think it is important.

I think there are some special concerns that we kept coming back to. I have talked about them a little bit. I just want to highlight the ones that we think are really the key substantive issues that we are dealing with, and I am talking about them substantively and not in terms of specific tasks. That is the disclosure of research results. In the human subjects arena, when people want results of something that is totally unproven in a research study, it tends to be called the therapeutic misconception. It is the idea that even though it is research that has some benefit, we might want to call it the

diagnostic misconception in our work. At any rate, one of the things our initial public comments showed, and I think this is going to be a continuing issue, is that there is going to be great consumer demand for information in the research phase. Even if CLIA says no, it is going to continue to be a problem and I think we need to deal with it.

So as you know, the issue of disclosing results in a study, where the test has not been done in a CLIA-approved lab is totally forbidden. One of the things we have talked about on our conference call is perhaps we might want to specify some sort of a compassionate use exemption, where this might be allowed. So I am just throwing out these ideas. If we did that, we would need to also stipulate what level of scientific validity technical accuracy we would want.

I think we have talked enough about multiplex tests. Then the final issue, this issue we keep coming back to, how to define and then how to review social harms--both of those things. First define them and then figure out an appropriate mechanism of review. One of the things we discovered in our consultation was that IRBs technically may not consider the social impact of research. Their mandate is to not look beyond the issues involving the individual subject, so they actually cannot say we want to sort of control this research because we think it might have an ultimately poor outcome for society, as a whole. Therefore, that is going to have to be at another level. So one of the things we might do is consider the mechanisms and other mechanisms and look more closely at the role of the FDA, because they also have not a lot of experience in this area.

I just wanted to highlight our tasks that overlap with other groups. We are going to have to coordinate with the data group in terms of developing these informed consent templates. And we have to coordinate with the education group in terms of the

IRB issues. So our next steps are as follows. We need to review the expanded scope of work with the full SACGT, and we are doing that right now. We need to set priorities and we are going to plan a one-day meeting, perhaps where we can begin to do a more formal review and endorsement or suggestion about the NBAC recommendations and to define the scope of our report. That report we had possibly--this was an outline that Susanne and Sarah put together in terms of what possibly might be in that report, if we do come up with some kind of a white paper report. It would talk about informed consent for different types of tests; how informed consent evolves as tests move from research settings to clinical settings; the challenges of informed consent for multiplex testing; and models of consent for different phases of genetic test development. Finally, to really develop the arguments behind why we feel there needs to be additional research about certain aspects of genetic tests and families. So that is that and let's begin the discussion.

DR. MC CABE: Thank you. I just want to make a couple of points. One is that, in the document that was received by the Secretary and therefore released to the public today, on page 30, we have actually already recommended IRB review for all research protocols independent of funding source. So I think we have really already done that. So we have accomplished that on your list.

Second, I think I mentioned that one of the briefings that I will be doing on Monday is with OHRP. That was because, as we began to see what was happening within this work group and within the whole Committee, we recognized that was one of the federal agencies that we had not included in the SAGCT or in the briefings. So after that briefing I think we will have much more information about desire to utilize us to help

with this. I would be surprised if there was not interest, given the work that has been done on that. So I think that will be moving ahead.

So with that, I will open it for discussion.

DR. FEIGAL: I would like to thank Dr. Press and the committee for some very thoughtful work. One of the things that struck me in the discussion, that you touched on briefly, but I don't know if any of us have grasped the full impact of this, is the phenomenon of consumers more and more seeking out their own diagnostic information and a phrase that someone coined is the information-empowered consumer. At a biotech meeting recently it was cited that Americans, when they are told they have a new diagnosis, 40 percent of them will actually log onto the Internet to try and learn about their diagnosis. There are chat rooms for all sorts of conditions.

When you were talking about the responsibility of the patient to be informed it is an interesting concept because in being an observer from the sidelines of a debate between a patient and her practitioner, the patient had concluded that she had heavy metal poisoning, from reading about the symptoms of heavy metal poisoning. She decided that they matched her symptoms and she wanted to be tested for platinum poisoning so that she could begin chelation therapy. She wanted a test which her physician refused to do. She actually wrote to us because she had used medical devices that she thought might be the source of her self-diagnosed platinum poisoning and wanted up to intervene and help convince her physician to test her.

The interesting issue was, did she have a right to find out her platinum level just because she wanted to know and make decisions based on that? The side sort of comment is that we spent about a day listening to issues around informed consent for

decisions made around implants which can be used either in a cosmetic setting or a reconstructive setting. The State of Missouri, for cosmetic implants, has a waiting period for informed consent. We asked the surgeons, do patients actually come back after that or not come back, decide not to have implants? The answer was, for reconstruction, often they will hear about the option and then they will decide not to have it. But in the cosmetic setting, the patients pretty much had informed themselves as much as they wanted to be informed and made up their minds when they made the decision to go see a surgeon and ask for the procedure.

Then it gets back to that sort of core issue of, does the burden of proof then shift to the physician? Normally the physician or the clinician or the nurse or whoever is doing the informed consent feels under the gun to show they have provided an adequate amount of information. Now are they in the position of having to assess whether the patient understands the implications well enough to be allowed to have the test and is there a gatekeeper role, which I think the public is sort of increasingly turning thumbs down on. And they are saying, if they want to know certain information, they have a right to it. It changes the whole dynamic very much. Those are not very well formulated questions, but they are comments if you want to think about them.

MS. BARR: I just wanted to speak because I wanted to follow up. I was struck by the notion of responsibility that Nancy talked about. I think there is an inherent bias in the words “informed consent.” What I think we are really looking at is informed choice. While I don’t think we are going to turn the world upside down by changing it right now, I would like people to think about the difference. When you ask for informed consent, you are basically telling the patient in a subtle way, we would like you to say yes

and we are just going to give you this information so you can. When you say informed choice or you say making choices, you are letting patients know, or research participants know that there are options. In following the really very nice work that Wylie presented on the template, it seems to me we might think about one mechanism of dealing with it and it would be just a partial way of dealing with it, again to turn it on its head and to say, what is the piece of paper we should be giving to the patient so that they have a checklist? Then they are in a position to check--Doctor, did you tell me this? Did I get this? Did someone talk to me about this?

That checklist could be given to them repeatedly so that when they are involved in genetic testing, they are being sure to ask the right questions. The burden is not on them to figure out the right questions, but they are being given a template so that they do ask the right questions.

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

DR. PRESS: Yes. First of all, hi, Pat. I very much agree with your point about informed choice. I think the point I was trying to make in the overhead, which obviously you could not see by phone, is that it is a matter of helping somebody make a decision and it is a decision about a choice, about a service, that is being offered. I think that is much more valuable than the idea of consent.

I also think in terms of the comment made before, and I am sorry that I don't know who made it -- I think there is a difference between a putative responsibility to be informed about a choice that you are being offered, and this other issue, which I think is a problem but a whole different issue about does a patient, a health care consumer, have a right to demand any kind of service that they want. I think the answer

is no, but I don't want to get into that.

MS. BARR: I think the example given, in many ways--I don't know the details of platinum poisoning--but many times patients know more than the doctor they are seeing. And it takes a long time for a patient to convince a doctor that they have good information and there is something out there that might be useful. And that happens, too. So I think we need to be careful. I know this inappropriate consumer demand, exists. But there are also appropriate consumer demands that are not always met.

DR. PRESS: I would agree with that, but I still think that both of those things are separate from the idea of whether or not a patient or a research participant may have a responsibility as well as a right to have the information and be thinking about it and making a choice that they are consenting to.

DR. PURYEAR: I found the presentation very interesting. But as a Committee, I think we should be very careful about doing informed consent broadly. Especially creating a template with the recommendation that it should be used broadly. I think what David brought up and even what Pat was just talking about, clearly the kind of informed consent you are giving, the process you engage in is really defined by the setting that you are in at the time. I am not saying that you don't always do sort of the same things, but I think that what is involved with informed consent, to inform the process, to get somebody to engage in research, is different from the kind of informed consent you need to have reconstructive surgery or engage in a surgical procedure. I think that what we do here can dictate in places we don't necessarily want that to go. So I think defining the area the Committee tackles is really very important and it seems very broad.

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

DR. KOENIG: I just wanted to respond that I think what Pat Barr asked for is pretty much what we were imagining in terms of the template. It would almost be more a list of what do you want to know in terms of the data that is available, in terms of genetic tests. Because of the uncertainty and the constant change in this field, I think there are actually commonalties across the research and clinical phase. Obviously it is going to be different in the research phase, but I think there are some commonalties. So I don't think we are trying to re-do all of informed consent, even though in order to talk about that we had to become somewhat generic. But we are very focused just on what is essential in the genetic testing arena.

DR. MC CABE: Dr. Khoury, and then what I would like to do is really work on helping the work group focus is efforts and determine priorities.

DR. KHOURY: I would just like to add to what was said and give you a bit of a quick update as I was asked to do on some of our efforts at CDC. I like what Nancy has done with respect to--you had a diagram where you started with gene hunting leading all the way to my favorite areas of epidemiologic research of prevalence and penetrance and some of the other things. I think as this Committee struggles with issues around genetic testing, I think the issues around informed consent, as we discovered from a public health agency that is further and further removed from individual patients or their families, but trying to define the impact of genes or gene variance on the whole population through a number of ways. We can do that through stored tissue samples like NHANES, et cetera.

I had someone in my office, a bright person who was working with Barbara, who took a very elaborate look at the NBAC recommendations and saw how

much of it is relevant to what we do in public health research, around large-scale population studies. The two areas which are a little bit different, as you move down that continuum, first you move from family studies to population studies. So the BRCA 1 type analyses that you do in a family context become a little bit different if you are doing BRCA 1 studies in the general population.

Second, you move also from the high penetrance genes to the ones with polymorphisms and where the risks are much lower. We have found that many recommendations are not quite applicable. In that context, we have been working--actually we started that process before you guys started this process and we have a few members of this group and others on the outside trying to help us put together a template for the kind of population-type research that will help shed some light on that progression that you added, Nancy.

Where would that be helpful to this Committee. I think the world of informed consent is big and what I would recommend is exactly what I recommended yesterday to the education group is to focus on the areas, as you began to do obviously, Barbara, on that continuum of oversight from 1A to 2B, et cetera. Then coordinating with the data group, with Wylie, on clinical validity and utility. What are the elements? I don't think you can go beyond broad recommendations. So I would stop short of creating actual templates, but provide some general guidance that you could give to OHRP and NIH and PRIM&R and CDC and all the groups. Maybe developing actual templates may be a little bit going too far, given how big the issue is and there are other groups that will be obviously tackling this. If you have any questions I would be happy to give you more information about that project next time we meet or between now and next time.

DR. LEWIS: I think this follows up nicely on what you just said, that to me part of what we are talking about is patient education of their rights and responsibilities. I thought you did a really nice job, Nancy, of talking about the issue of informed consent right versus responsibility. I think a lot of times we talk about it from the perspective of the professional, in terms of what are we needing to do to make sure we are practicing safe and effectively, but I think if we turn it around and look at it from the perspective of the consumer, in terms of what do they need to do to be safe and cognizant consumers of health care, that that becomes the issue. So to me, this fits in with the patient education piece of the education task force. I am not sure a template is important as much as what I heard Pat Bar saying, what are the issues you need to know in order to be an informed consumer?

DR. MC CABE: Let me comment about templates, because one of the ones that was contributed was one from UCLA. The reason why we undertook it was that we recognized that research involved in genetic information received a very different review if the protocol identified itself as genetic or if the PI was a geneticist. But if another individual was doing genetic research but naively did not mention it was genetic, they didn't really have to address the same issues that the geneticist had to address. So we actually developed a template to inform the PI and to help the IRBs -- we have two different IRBs -- recognize what the issues were. So it was intended as educational. It seems to have accomplished that purpose.

Very interestingly, before people were ducking the genetic thing. They would avoid using genetic anywhere in the protocol and to try and duck out. Now people are identifying with genetics and using the templates, even when it is not genetic at all.

So perhaps we have raised the consciousness a little bit too high and now the IRBs are trying to instruct what the boundaries on the other side of genetics are. I am not saying this in a defensive fashion, but there is an educational role that doing this sort of thing can accomplish. I would like to begin to focus on priorities now and help Barbara and the committee with the priorities. What about the white paper concept?

DR. BURKE: I think we already heard from Muin and Judy and I would just echo the same thing. The priority, if we think about the central work we are doing on this Committee, it seems to be the way the informed consent group interacts with that is in something I will call a checklist instead of a template. It seems to me what we are saying in not a model consent form but a way to be sure you have covered all the areas that should be covered. I think the white paper--I would defer to the group in terms of the best mechanism--but I think they have decided a white paper might be a good mechanism. I would just say focus it on the checklist, focus it on the rationale for the checklist and have a good dialog with both education and data committees. That is, it seems to me we are all helping each other to stay in a central focused area. That should be the same focus also for data and education and access.

DR. CHARACHE: I was very concerned about the issue of disclosure of experimental results to patient subjects. One of my concerns is the fact that many of the researchers, very good ones, sometimes have set up their study design in such a way that the analytical validity is at high risk. So if we are going to have a white paper and advise IRBs, I would like to be sure there is a review of their laboratories and some understanding that the answers they are putting out in fact have relevance to truth.

DR. PRESS: I would just like to clarify what I meant, because I realize

there are CLIA problems and I also realize that results may be meaningless and may be over-interpreted. I think what I had in mind more, and it was shaped by some of these experiences that I have been in, like the one I talked about, a collaborative interaction with the families where the research is being done. It may not necessarily even be individual results as much as explaining to the family where things were at, what the meaning was, and what is going on, where you were. Not to necessarily use the term analytic validity, but what the progress was step by step, not necessarily returning results to individual people. I think what people really want is not to be left in the dark. I think they feel they have given a lot, that they are collaborating, that they are sharing and they want to know what the thought process is. It is kind of its own version of transparency and informed consent, just letting the family know what is going on.

DR. CHARACHE: I think it is very important that the subjects be partners in the advancement of information. But I am very concerned, even if it is compassionate, the investigator may feel compassionate but may still have wrong answers.

DR. BURKE: I just wanted to follow up on that and agree very strongly with what Pat said. It seems to me that, to the extent that the informed consent group has identified giving results back to subjects as an important topic, it seems to me that any discussion of that needs to include a clear understanding of the rationale for the requirement that a lab be CLIA-certified. So any discussion of a compassionate use exception ought to include that there needs to be evidence that the lab is in some fashion addressing the concerns that a CLIA certification would address. I agree that is an appropriate piece to consider here.

DR. BOUGHMAN: I would just like to concur with the comments. I

think that a draft white paper from the team or work group to be circulated and come back to this group, as was requested from the education group yesterday, seems like a very good idea. I will say, no epiphany overnight, but I don't want to let you down. I did come up with a diagram so the things are coming into some focus here. But in fact it was one of Barbara's comments yesterday and Muin's idea, the diagram of the steps of the process and identifying potential action points or points at issue, or groups that need to be focused on. In our situation, including the professionals, the consumers, or patients themselves, and then more generic public issues. But IRBs came in at two or three places there. So I think we are beginning to converge.

What this has done for me is allowed me to think about ways that we might address the issues without doing the research or coming to the absolute conclusions even without doing the research ourselves. I think sometimes that is difficult to come up with, but this kind of format I think can work.

DR. KOENIG: First, is there anyone else on the informed consent team who wants to comment? I realize in the other talks we asked other team members right off the bat if they had any comments. We didn't do that today. Okay.

I think we do need some more help with priorities because we came up with quite a list. I think some of the activities like endorsing certain NBAC things would actually not be very time consuming and may have a lot of rhetorical use in terms of moving forward a particular agenda in this area. But Kathy, before you comment let me just say, I recognize, Ed, you said we had said that we want IRB review of all tests. I understood that. But the issue of whether we would also go on record as supporting NBAC that was specifically a strategy of moving forward this agenda, even though it

duplicates our own previous recommendation, or maybe pointing out that we would also recommend that.

DR. MC CABE: Kathy, and then I may ask for clarification--Kathy, you go ahead. You may clarify the point I had.

DR. HUDSON: I would have some concerns about us evaluating the NBAC report and either making a judgment as to endorsing it or recommending modifications or throw it out the window for the wrong reason. I chaired a group at the NIH when the NIH commented on that report, and it was a full time activity for four months. So I would actually not recommend that we do that because it is so time consuming. In addition, there is a group in the Department now that is evaluating that and I think the outcome of where those reports are going to go and their ultimate impact is very uncertain. So I would put that as a low priority rather than the other.

DR. KOENIG: We weren't suggesting the full report, by the way, just about three or four specific recommendations.

DR. MC CABE: In addition, one of the things I learned about protocols, and it has to do with reporting structure. We probably as a group, could not do that independently. That would have to be vetted through the agencies and it has to do with who NBAC reports to versus who we report to. So there are technical issues about such a thing as well that we would have to look at.

DR. FEIGAL: Just two things that the subgroup might consider that we discussed before. One of them is whether or not there is a useful role for central IRBs, given that there is the separation often in time and space between the testing laboratory and the clinician or the patient who is ordering the lab tests. It is usually the person

ordering the test who has to have the informed consent, that has to have their local IRB approve it. But if you have a test that is not ordered very frequently, that is going to be used 500 times in 500 institutions, then having a central IRB plays a role in how to do that. It might be something--there are examples of that. So that is just a topic to suggest a little further exploration.

I also think we really should look at direct-to-consumer advertising for these tests. Anybody who has seen a Jewish newspaper knows that there are dozens of tests and there are ways to get them. Thirty-five states allow people to walk into a lab and request that a test be drawn and the results be sent to them personally. So the only real leverage is at the laboratory for them to look at what they think their informed consent services are and how do you do that at a phlebotomy center for a laboratory and what is the process? So is there a standard of information, of patient information knowledge that this group could comment on that they think would be appropriate when laboratories choose to do direct-to-consumer advertising.

DR. MC CABE: Regarding the central IRB, I think this is a very important issue and it gets to the issue on rare diseases because with the requirement that is being enforced now, that if you do research on your campus you have to have IRB approval from your IRB, it means that for these rare diseases, where it used to be that we would use the consent form from another institution, get the consent of the patient and then mail the sample to the one lab in the world that did that, now the burden on the clinician to get IRB consent for that becomes a significant issue.

DR. KOENIG: I may point out that is one of the specific issues that NBAC is dealing with and it is those kinds of dilemmas that I was hoping we could

simply tag onto people who had spent a lot of time thinking about those issues. Because one of the sets of recommendations that we are currently debating is the issue of having review from multi-site research by a single IRB. So I am now feeling a little bit in a bind in terms of whether or how we should proceed independently versus as part of the group.

DR. MC CABE: One thing that I mentioned to you and to Kathy is the NCI model. When you have a cancer center, NCI requires any study involving cancer research, whether or not it is funded through NCI, to go through a parallel review, basically a pre-IRB review, and whether that again might be another way of looking at genetic testing and trying to make sure there was some uniformity from institution to institution. I think it is another way of looking at the central IRB as well.

DR. BURKE: I just wonder, on the NBAC issue, it seems to me what I was hearing that it is probably not a good use of our time, nor perhaps something we even have the authority to do, to comment on NBAC's recommendations. But it seems to me there is a different issue, which is maybe the one Barbara was just getting at and that is whether it might not be appropriate to look at NBAC's recommendations in relevant areas and ask whether there are particular issues of application of those recommendations that are important for genetic tests.

DR. MC CABE: I think that is a different way of dealing with it, rather than saying we endorse, look at what the recommendations are and then adapting those to the charge of this Committee.

MS. CARR: Are you suggesting we do that? Continue that with the several recommendations that Eric Meslin identified?

DR. BURKE: Yes, it seems to me that the tenor of this conversation is

that the core issue and the highest priority is the checklist, what do people need to know, and we have now identified two other areas that are extremely important. If I am hearing this right, one of them is data back to subjects and the other is informed consent in the absence of the health care provider. It would seem to me that any NBAC recommendations that shed some light on those issues and can serve as a basis for commentary on specific issues for genetic testing would be appropriate. But it is kind of up to the informed consent group to determine whether that is the case.

DR. MC CABE: Joann, I am going to give you the last comment before I return to Barbara and then we will conclude this discussion.

DR. BOUGHMAN: I would just encourage the work group to use all possible resources, not unlike the education committee is capitalizing on NCHPEG and other professional organizations for work already accomplished or in progress. I think that the NBAC work as well as other organizations could be capitalized on in that respect, so it is clearly not an endorsement, per se, but background and information gathering.

DR. MC CABE: Thank you. Barbara, any last questions to the group? Do you feel you have some priorities?

DR. KOENIG: What about the issue of working with the Office of Human Research Protections.

DR. MC CABE: We are going to be briefing them on Monday. Part of the purpose of that was to let them know what we were doing, find out what their plans are and see what the relationship might be.

DR. KOENIG: Okay, so we will hold on that.

Next Steps/Discussion of Other Issues

DR. MC CABE: We will know better after Monday. Okay, thank you very much. Thank you, Nancy, for an excellent, informative presentation and for the working group dealing with these issues.

We now have about an hour to deal with three issues. If we run over a little bit, some of you may be able to stay. I hope we won't lose too many. Let's see if we can get it done in an hour. We have the model to deal with. Wylie, do you want to go ahead? I know you have been working on this since this morning. And look at the model again. This does not have to be considered the final absolute model, but something that we are fairly comfortable with beginning to try out.

MS. BARR: Is there a fax machine somewhere. If this isn't an overhead, it could be faxed to me.

DR. MC CABE: I am sure we can get it. We may have to fax it off of the overhead.

MS. BARR: I don't want to interrupt you guys, so I can just listen.

DR. MC CABE: We can run through it.

DR. BURKE: Yes, we will walk through it. I actually want to say this. After our last presentation there was a lot of conversation at lunch, so this came out of a lot of conversation. Several people around the table have contributed to what is not a very simplified version and I am just going to go through it very quickly.

I think we have consensus for the first three steps of the pathway, if I understood the conversation earlier. What we are saying is the first question is, does the

test have analytic validity, yes or no? No, the test is rejected. Yes, it continues going through the classification pathway.

Question number two--is the test being offered for population screening? Is that the claim? If the answer to that is yes, it goes to level two scrutiny. If the answer to that is no, then you get to the next question. The next question is, is the test a test for a rare disease? I have put down the working definitions that Ed proposed to us--1 in 2,000 prevalence or 1 in 10,000 incidence. There can be discussion about that, but I think there has been consensus that is an appropriate question and if the answer is yes, it goes to a level R scrutiny. That is a scrutiny procedure that is adapted to rare diseases. If the answer is no, we then go to the next level, and that is where all our discussion was last time. Our discussion really had to do with do you go to a checklist? Do you keep predictive versus diagnostic? If you do, how do you define predictive and how do you define diagnostic?

So what we have, compliments of David Lanier, is an attempt to define diagnostic to get us through that loop. The proposal is if, after you have passed the first two steps of population screening and rare, if the labeled use is only for the diagnosis in a person with signs or symptoms of the disease, if the answer to that is yes, we are using that as a definition of diagnostic, then you go to level one. If the answer to that is no, you go to level two.

I want to point out some of the elegant simplicities of this approach and also what we did with the checklist, because that was a point of conversation before. The really nice thing about this definition is that although there is some ambiguity in any definition you care to use, this is probably less ambiguous than anything else we came up

with. It is very important to note that we added signs and symptoms. It is not just someone who has an overt symptom. It is someone who has a clinical finding conceivably for the purpose of diagnosis. This completely sidesteps getting into special categories for prenatal diagnosis. They automatically go with all the other tests that are not diagnostic and someone who has signs and symptoms into level two. That gets me to the checklist.

It occurred to us that implementing the checklist, making the checklist operational, was really creating a level of review. That is, no matter how good your definitions were of what is an intervention, what is positive predictive value, what is a social harm, what you are doing is creating a whole other level of review. So out proposal is that is part of level two review. So what happens is, if the answer is no to this, is it labeled only for diagnostic use, then it goes to level two and presumably one of the early things that happens in level two review is some operationalized version of that checklist. And there will be some things that go through that checklist quickly and easily and get, therefore, through level two quickly and easily. And others where you identify the problem with the checklist.

DR. MC CABE: I notice one thing you have put level R on the same side as level two. Before it had been over on the side that was more like a level one.

DR. BURKE: That has no importance. It is just space on the paper.

DR. MC CABE: The other thing I want to mention is that we will make a copy of this and fax it to Pat Barr when we are done. We will make copies of this and make them available to the people here in the room because we would like people to try this out or whatever we derive from it.

DR. CHARACHE: This I don't think will answer the problem of making everything level one. There is no control over off-label use. So if any clinician or any body of people want to recommend that this test be used for predictive purposes, all the laboratory has to do is say that this test has been approved for diagnosis only. So it will still dump everything into level one. That is not answered. I obviously think it is a little harder to define. I think we can define it, but I like the numeric concept of saying what the predictive value is as a break there, rather than letting everything go through as a category one and then evolve, as cystic fibrosis and Tay Sachs and all the rest have, into predictive value when they first started as the intended use being diagnostic. I still think that is a very huge loophole and I don't think it is necessary because there would be so few diagnoses that get down that far for the points that were made, as Muin said. So I think this is a high risk step to that concept.

Secondly, I would like some way of expressing the fact that this diagram is limited to genetic tests. If you go this route again, it opens up a floodgate for all diagnostics, if all they say is that it is for intended diagnostic use, which most tests are.

DR. BURKE: Point of clarification in your comments, Pat. Are you proposing that the way to fix the problem you have identified, which is too many tests will get into level one, is to keep the requirement of labeled use only for diagnosis and add an additional requirement about positive predictive value? Or to use positive predictive value in place of the labeling requirement there?

DR. CHARACHE: No, I don't think a labeling requirement will do any good in terms of being sure that predictive tests don't go through as a one. I think the only way of doing that is to not have that as a criteria, but have surrogate criteria. As we

pointed out, we tried to think in the Genetic Forum of any test that would be diagnostic only and we couldn't come up with any. They are all both diagnostic and predictive. Secondly, if we use the suggested definition of rare diseases, we could only come up with one, which you pointed out today, only one entity that would ever get down to that box. So I don't want that box there to dump everything into level one. I don't think it is necessary and I think it is very risky.

DR. MC CABE: I would point out that my understanding of the discussion in the forum was that everybody was concerned that everything went automatically to level two review and that would create a bottleneck.

DR. CHARACHE: No, it was the other way around. They were concerned because all eight models that we worked with turned out to the both predictive and diagnostic. That if they could come in with a diagnostic use, it would be used for predictive off-label.

DR. MC CABE: The e-mails that I got that were on fire as they came onto my screen all indicated the concern that it would be a huge bottleneck and the problem was the level two. But I just know the e-mails that were sent to me very angrily after that meeting. So part of this was, I thought, to try and avoid that.

MR. HILLBACK: Two things. Pat, I think you are still trying to manage clinical practice by managing labs. I don't think we can do that. But I had a question back to Wylie. When you talk about signs or symptoms, or when David came up with it, whoever, where are we on the situation of a disease where you have had two or three sibs in a family that already are affected, you have these early onset diseases like a Pompe or Fabre, some of the ones I am familiar with in metabolic lysosomal storage disorders. You

want to do things as quickly as you can pre-symptomatic. You are really not talking about these things as being predictive in that sense. They really are in that pre-symptomatic stage and maybe we are back to taking this now as a framework and going off and trying to define better definitions of what signs and symptoms are, rather than argue about the shape of the box.

DR. BURKE: I think there are two points there. The first is that there probably is a correlation between high penetrance and rarity. It is a crude correlation, but it is a correlation nevertheless. So a lot of the examples you are going to bring up that are going to be a concern are in level R.

The second, though, I don't want to sidestep that there is ambiguity. Even when you say signs and symptoms you then have to define what you mean by signs and symptoms. I actually think the hemochromatosis example poses that problem. Does a family history of hemochromatosis represent a sign that makes HFE testing for the same genotype diagnostic in the sib? That has to be a consensus decision.

DR. KHOURY: Actually, as I think about how it has come around, there are several issues that need to always be considered. I like the simplicity of this. When I presented the model yesterday, which essentially looks exactly like this with the exception that we have defined diagnostic versus predictive, and in my instructions to people at CDC who looked at the 800 tests, they asked me what do you mean by diagnostic versus predictive. I think I gave them this kind of definition. Think about diagnostic as somebody coming in with signs and symptoms and consider everything else in the other box. So essentially we have a preliminary test of this model as I presented to you yesterday with the diseases that fell out in those categorizations. Now the rare

disease assumption, I don't know if this will affect much but we go back and look at it.

In answer to Pat Charache, actually there is no way that I know of to prevent off-label use. I think everybody comes in with an intended use and you get reviewed and you get labeled according to the intended use. That is where the pre- and post-market analyses will have to be carefully coordinated. We heard yesterday from the FDA that occasionally people come back for re-review based on wanting to use the test for other purposes, I think with PSA. But we can fairly assume that with genetics it is not going to happen. So the group has to decide how to deal with that. But I think it becomes sort of what Elliott said, the practice of medicine. On the other hand, forcing things into some kind of a priori labeling that applies to genetics, knowing all the issues around it, would be essentially very useful. As the post-market phase becomes more advanced and evaluation of tests for different intended uses by different professional organizations--think about hemochromatosis and CF as they come in first to diagnostic use and then people want to use them now for populations screening. Then they become level two, but it is too late for that FDA initial pre-market phase. You activate other processes like consensus development panels, like we did with NIH and CDC, and it becomes a post-market type analysis. We always have to keep in mind what you can do in the pre-market phase versus the post-market phase. Also the FDA can do a lot in the post-market phase if they want to exercise that authority, I think.

DR. MC CABE: Okay, Pat Charache, Joann and Francis--please very brief because we have two other topics to do. When we are done with the three of you I am going to ask the group to vote on whether we utilize this model and field test it or whether we try and continue to make changes.

DR. CHARACHE: Brief comment and two suggestions for improvements. One comment about the fact that everything would land in level two with the Genetic Forum. Remembering back what happened, in that particular one there were two separate boxes--predictive, which went to level two, and diagnostic, which went to level one. Because they were all predictive, it is true they all went to level two. In this case we only have one box which is different. That is, if it is diagnostic it goes to level one, but it doesn't have the other box that was there before. So that clarifies that, even though it is implied. That is why they all went into two, because there was that other box that said is it predictive.

Two recommendations for addressing some of these things. I think if it does not fit in the diagram itself, that we can put a statement that begins the whole diagram and the reason for it is that this diagram is designed for genetic tests only. That then removes some of the precedent pressure.

In terms of that box, I think what would answer it, and I don't know how the FDA would address this, which is instead of emphasizing that you have to be symptomatic, we can get around that, plus my concern about predictive, by making that box say, if unlikely to be used for predictive testing. If we put in something like that, first of all, you have to remember that that whole box has only one entry in it. There is only one disease in there. There is going to be almost nothing that is going to get down to that box. The FDA is not going to be flooded if we have a restrictive definition there. There is only one disease that we know of. Almost nothing will get there. So I don't think it will matter very much as long as we have that R section. But we make that box dump towards level two. I would like something in there that would head it towards level two

is it if going to be used for predictive.

DR. BURKE: I think the issue that we are dealing with here is really how much complexity we can put into the test classification. I want to reiterate that one of the concerns that led to this particular approach, which clearly may not be the best approach, was to avoid creating a checklist process that itself was a process of review. Even though what Pat just proposed is much simpler, it calls for what would be, in the end, a fairly momentous decision to be made as part of a test classification, that is, a judgment presumably made on the part of somebody reviewing the paperwork of a lab test that comes in that is billed as a diagnostic test, but is judged by someone--who would that someone be at what point in the process--as having potential for predictive use.

So it gets back to something else I think is very important. Do we do the test classification based on claims of the test offerer or do we do the test classification based on some judgment of materials as they come in? If it is the latter, we have made the test classification system itself more complicated, that is, involving work, judgment and all the things that are involved in people questioning that. Frankly, I would find it simpler to just say if the answer to rare question is no -- level two scrutiny.

DR. LEWIS: I think in Ann's absence, I might suggest her idea before lunch, and that is the inverse of what is in that box right now, which would be, is there intended use for patients with no signs or symptoms of disease? If the answer is yes, it goes to level two. If the answer is no, it goes to level one. I think that keeps the simplicity. It keeps us away from the term predictive and it shifts the tests that fall in any gray zone and some of the judgment calls slightly in the other direction.

DR. CHARACHE: How do we handle family members where one person

is symptomatic and the sibling is not?

DR. Mc CABE: The recommendation was to ask the question the converse of this. Is the intended use for individuals who do not have signs and symptoms of the disease.

DR. COLLINS: I apologize for not being part of the early part of this conversation due to a host of other things that are swirling around the genome office as usual, but from having talked to Wylie yesterday about her idea of trying to define the difference between predictive and diagnostic, and knowing that you all discussed it earlier, I am sorry to hear that it got displaced by this definition. Because we don't know how to define diagnosis--at least I sure don't--and we have struggled with this in other settings, like legal constructs for months and months and months. It is very difficult. I don't know how to define a sign. Some people would say a DNA sequence variant is a sign, so it becomes rather circular. If you have a sign or a symptom that counts, then everybody has a sign of some sort. I would much rather see a definition in that box that did not require four more definitions that are difficult to write. Is a pharmacogenetic test diagnostic? We had this discussion yesterday and there clearly was some disagreement about that. You might argue that in this circumstance it would fit that definition--diagnosis in persons with signs or symptoms of disease. But I don't think that is what we would want to have pharmacogenetics do as far as its traveling on the path here.

So even though I gather it did not carry the day because it was a little quantitatively troubling, I would like to come back to this positive predictive value definition as the thing that really is the thing we are trying to say. So why don't we just say it in that box? Because that is, in my mind, the difference between a test that ought to

go to level one and ought to go to level two.

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

DR. BURKE: This was an alternative. What this modification says is once you get past rare, ask about the predictive value of the test. Don't ask whether it is going to be used in symptomatic people or un-symptomatic people. Just ask about the predictive value of the test. Don't focus on 95 percent. The number could be modified. That is not the point. It is a positive predictive value criterion. What we are saying is if it has high predictive value, meaning there is a lot of certainty that a person has a condition if the test is positive, then maybe that defines the test that should have a streamlined review. Then if the answer is no, clearly we have the issues of defining what we mean by social risk or social and medical risks and if we go back to our original terminology. We would get into those difficulties. If this is acceptable, then there would be two ways to deal with this. Either we would say, no we really are going into level two review and the first stage of level two review is the checklist, or we would figure out some way to operationalize the checklist. I think that is the alternative you are describing, Francis.

DR. GUTMAN: I think we, at FDA, probably by being silent and not having a clear vision of level one or two, certainly not a clear vision of level R, since that is brand new, may have confused things. When this model was first put on the table it was aimed at keeping the population of high scrutiny as small as possible so that they could be directed into a traditional review and looking at some expanded review for the vast majority of tests is not the way this is quite working out. We are quiet innovative.

I just have to make a couple of comments here. One is that Wylie is correct. The positive predictive value assumes you already know about the test and you

have already reviewed it. Pat is also correct that they will game it and they will all be diagnostic. But I am telling you they will also game it and they all will have a predictive value of a positive greater than 95 percent because they will study it in a subset of populations where it will be very high. So my recommendation would be to go back to what I think Pat was suggesting. Let us try and adopt a model maybe to where you are--let the rare be the floodgates and if you are worried about the difference between diagnostic and predictive, put them all in the same scrutiny and figure out a way to review then evenhanded.

DR. BURKE: So you are talking about after you get to rare and the answer is no, you go to level two.

DR. GUTMAN: And Lewin claims he has modeled it and that is a safeguard. That a lot of them will in fact be driven off that way and then you don't have to argue about this. Or the other thing is to leave the predictive and diagnostic and stop worrying about the off label and the gaming because I am sure it will occur and you have to live with it. That's all. If you worry about everything or if I worry about everything or if Dr. Feigal worried about everything, all of us would have nervous breakdowns.

DR. MC CABE: But I also worry that if we worry about everything we will get nothing accomplished.

DR. PENCHASZADEH: I think Steve just clarified some of my thoughts. I was about to sound very heterodox here, because if we have so many difficulties in classifying diseases by frequency, complexity, predictive, diagnostic and so on, unless you know exactly what is going to happen at level one and level two, we cannot really make a decision. So my point is, revisit the question of the levels, the high scrutiny and

the low scrutiny. Perhaps what was just said, one should have a minimum set of criteria to scrutinize all those tests.

DR. KHOURY: I can assure you from a practical perspective, I think this fine tuning that we are doing now are not going to affect substantially the current 800 tests that are on the market. Whatever we do today is still going to leave us with a small fraction of the tests in level one or R, because of the rare disease situation. I think an interesting twist to what I see right now is that there are two reasons why things are pulled to level two. One, if the test is going to be used for population screening; and the other reason is you are dealing with a genetic test for a relatively common condition. So now it becomes two versus R. There is not really level one. That is the simplest classification you can think about--rare disease, provided it is not for population use basically, like newborn screening. Then the rest of the world becomes level two, which then would require the FDA to think about the safeguards and the proper review. From a public health model this fits because then we can ask all the issues about predictive value, social issues, et cetera.

MR. HILLBACK: We have a lot of definitions we are trying to deal with. I am trying to process what Muin just said. I guess until we know where FDA comes out, I don't know whether to argue with Muin or agree with him. It might be a great idea. It is really a function of the paragraph that I think Francis inserted some number of meetings ago about can the review be done in a way that does not increase time usually and increase cost usually so as to limit the creation of new tests. It is hard to know with this decision rule until we see their system. So I can't really argue against what Muin just said.

DR. MC CABE: I would say again, this is a model that would be tested.

DR. CHARACHE: I would like to support Steve's recommendation considering two things. First of all, it gets the high use test either because there is a large at-risk population or because it is being used for screening of populations. Then you go into the low risk with your Rs, which will undoubtedly be RA and RB, which the group will then have to look at.

The second reason I like it is because it won't take so long to triage that you are wasting a lot of time that would be spent on review. It is very simple. It is population screening low volume test, and that is the end of it. And you don't need a geneticist to make the determination of which group it goes to.

DR. MC CABE: Okay, so we are now going to decide whether this is the model we will go after. If we decide it is not, I am not sure what we will do because it is getting very late and people are going to be leaving soon. Basically the model would be you had analytical validity, yes/no. If it is no, it is rejected. If it is yes, it goes on to a question population screening, yes/no. If it is yes, it goes to level two. We think that will occur fairly rarely. So no, then it goes to rare--yes/no. If it is yes, it goes to level R and if it is no it goes to level two. That is pretty much it. That would allow Muin to do the modeling. We would like the companies--I know that Genzyme had done some of this before, but we would like input from the other companies as well, if you would. Francis, very briefly.

DR. COLLINS: A friendly amendment if this is the algorithm--could we just redefine level R as level one?

DR. MC CABE: It becomes level one.

DR. CHARACHE: No, some of them will become two.

DR. MC CABE: There is no level one. There is level R or two.

DR. CHARACHE: RA and RB.

DR. MC CABE: We will give you a chance to redo it neatly to hand out to everyone when we are done.

All in favor of the model as proposed on the overhead, a very simplified model which is basically rare versus population screening or common disease. All in favor, please raise you hands. Wait a minute. Let me see if we have a quorum--I see seven. We have a quorum. All in favor of the model as shown, please raise you hand. I see seven. All against? None. Abstentions? There must be someone who abstained--one. Okay, so it carries as the model that will be tested. I thank all of you for your input on this.

We will pass it out quickly. Wylie will make a neat copy of this and we'll get xeroxes of it on the table and passed around the room so everybody can have them to look at.

Patent letter--what I want to accomplish in about 15 minutes is that we decide in general, with sufficient detail that Sarah and her staff, along with me, can take it and turn it into a letter, sign it and get it off to the Secretary, and not wait until February. There is some urgency in trying to get this out very quickly, or perhaps not even worrying about this.

We need to look at the Hillback copy.

MS. CARR: There were two who came up with suggested changes, Hillback and Davidson and they are reflected here.

MR. HILLBACK: I would just, sort of by way of comment, I felt it was

important to focus this on what we really were aiming at, which was it is an access issue from our point of view. It is not, per se, a patent issue. It happens to be around patenting and licensing. I think we had a consensus, but I wasn't sure, that we would take out the Canavan's example and then the only other real significant change on my part was to suggest that a lot of the rhetorical questions in the last paragraph were sort of leading the witness and I would just as soon not do that. But still raise the issue that this did cause concerns, but that patents and licensing was going to happen and possibly the Secretary would need someone to take a look. I don't think it is a fundamental change in the meaning of the letter. It was just a series of edits to tighten it up a bit.

DR. MC CABE: In the re, would you still say re gene patenting and licensing?

MR. HILLBACK: Yes, access issues related to.

DR. MC CABE: Yes, access related to gene patenting and licensing. We had discussed removing the Canavan, and as I recall the discussion, people were in agreement on that. I agreed. I was concerned about leading the witness in the questions. We were definitely leading the questions down a logical path that imply some conclusion toward the end. So I think that makes sense. There is an issue that there is a perception--if you go to the second paragraph, second half. It starts "there is a perception that commercialization approaches may affect accessibility." Is everybody comfortable with the word "perception?"

MS. CARR: But also particularly, he took out "quality." I know that was an issue for Pat Charache. This is in the third paragraph.

MR. HILLBACK: Quality is in there once, but it is not in there in that

place. It is further in the last sentence.

DR. MC CABE: Having to do with the development of quality assurance programs.

DR. CHARACHE: Could I comment on that? I actually had a sentence I would like to suggest go in there. Sorry I did not turn it in earlier. But I would like to add a sentence that says, "Assurance of continuous test accuracy is compromised by limiting the ability to perform comparative testing between laboratories or develop proficiency testing."

DR. MC CABE: You don't see that is already in there?

DR. CHARACHE: No, it is not. The only thing that is in there is the single word quality that does not explain why the quality is compromised. Because that is what happens now. You send samples to multiple labs and people get the same answer as you have.

DR. MC CABE: This is also a perception on some parts. Do we have any data to support that. You have made it as a positive statement, a statement of fact. Do we know that?

DR. CHARACHE: We don't know that for every test that is done now, this is correct. So maybe we could say it may risk.

DR. MC CABE: Okay, if we could put it in as a qualified, I think that might reflect--so maybe if you want to work on that.

DR. CHARACHE: I think that is wiser.

DR. PURYEAR: Why doesn't the last sentence serve that, because it raises concerns about the training specialists who offer genetic testing services in the

development of quality assurance programs?

DR. CHARACHE: I was looking at that more as people, as opposed to being able to do comparative testing.

DR. BURKE: I appreciate that the tenor of the conversation, when we had our presentations, was to suggest that licensing was the problem. But I also want to say that we don't know enough to make a judgment whether the problem is gene patenting issues or gene licensing issues. I am comfortable with most of the changes that have taken out gene patenting. For example, I am very comfortable with the first sentence of the first paragraph, removing gene patenting from the discussion. I am comfortable with the removal of the phrase gene patenting and licensing from the phrase in the middle of the second paragraph. But I think the third sentence in the first paragraph should not be changed. I think it should remain, "However, through consultations with the public we have become aware that certain gene patenting and licensing practices may be having adverse effects on accessibility to and cost and quality" et cetera. The reason I say that is I don't think we should set ourselves up to know whether the solution or the problem, or if there is a problem, is in licensing or patenting. We just don't know.

DR. MC CABE: This is not something to arm wrestle over. Personally I think we have heard from lots of people that the patenting side is really a third rail and very difficult to influence. If you want to throw that back in, I am not going to fight over it.

DR. BURKE: I agree. I mostly want to say we don't know. I don't want to imply that we make a judgment on it.

MR. HILLBACK: So we can put it back the way you did. I think that is

fine.

DR. MC CABE: You took involving genes or tests out, but put it back in front.

DR. BURKE: And leave the phrases patenting and licensing out in the other places.

MR. HILLBACK: That is fine.

MS. CARR: I would suggest that you leave it where it appears in the second paragraph because that sentence is simply describing the session we had in June, which was called gene patenting and licensing issues. I don't think we should recharacterize that.

MR. HILLBACK: That is in the fourth line of the second paragraph?

DR. MC CABE: Yes, fourth line of the second paragraph, restore that as well. Mary, would you accept these changes to the letter?

MS. DAVIDSON: Yes, and I just want to go back to Elliott's first sentence because I really preferred it. I only offered another sentence because I wasn't sure that everyone would agree emphasizing access, but I think that is what this Committee is all about.

DR. MC CABE: Okay.

DR. PENCHASZADEH: Going to the last paragraph, change adverse effects for access issues. I think that our main concern is that of possible adverse effects on access. I think the letter should express that and I would propose that it say possible adverse effects on access.

MR. HILLBACK: That is fine again. What was concerning to me was

adverse effects was undefined. If we go back and say adverse effects on access B

MS. DAVIDSON: Is it okay if I go to mine? I did have one other suggestion in paragraph four.

DR. MC CABE: Yes, there is also a copy of yours, Mary.

MS. DAVIDSON: This relates to whether or not I weigh in on adverse effects versus Elliott's more benign wording. I think it is important that the question be raised about whether there are in some cases, and again this has to do with some rare disease tests, whether there are beneficial effects of restricted licensing in some cases. That needs to be stated.

DR. MC CABE: If we take all the rest of the questions out, is there a way to put it into Elliott's form?

MS. DAVIDSON: I am sure there is a way.

DR. MC CABE: You could make it a statement after the fourth line of paragraph four, rather than a question. So can you work on that?

MS. DAVIDSON: Sure.

DR. MC CABE: Okay. With that change, so there will be Mary Davidson's question restored as a statement in that fourth paragraph, and also recognizing that we need to review it because I have already seem some typo and grammar things in here, is the Committee comfortable on voting on whether this would be satisfactory to move onto the Secretary? All in favor of this letter moving forward please raise your hand. I count seven. Any opposed? Pat?

MS. BARR: Here, but I think I better abstain.

DR. MC CABE: All right. It is hard enough for us who have it in front of

us to keep up with it. And the chair is not voting except in ties. And we have a quorum. So we will move that forward.

Our last item is priorities. What we need to do now is begin to look at the priorities that have been discussed and see if the Committee is happy with them. These are ones that have been extracted from our discussions.

So, the Data Team--continue outreach efforts including health professional organizations, develop definitions, and finalize the data template and present at February meeting. Are you comfortable with that?

DR. BURKE: I will just comment that I think the issue of definitions is a much smaller one now with the simplified classification system.

DR. MC CABE: But you will still work on that because there is still the issue of populations and rare versus common. And there is also the issue of mutation versus disease that is not trivial as one gets into it.

The Education Working Group--develop a white paper summarizing current efforts in genetics education, identify where gaps/needs are and make recommendations for how the Secretary could address these gaps. I think there was consensus on this. Does anyone disagree with this as the direction? The chair is comfortable with this?

DR. BOUGHMAN: As long as we realize this is a draft that the Committee would in fact make the recommendations.

DR. MC CABE: Yes, everything would come back to the committee. Not a simple technical issue, but just the way we do business, it has to come back here so that it can be done publicly.

Rare Disease Testing Team -- consider special issues of orphan diseases, mutations and other low volume tests; regarding access and cost issues, survey rare disease groups and test providers/laboratories about scrutiny level one/two regarding impact on access, considerations of low volume/low prevalence criteria. I think some of these are going to be altered by the discussion we had today, so really part of this has to do with looking at the model we developed and looking at the rare diseases and how they fit in with that model and special issues about rare diseases, if I can summarize them. Does that make sense?

MS. DAVIDSON: Yes, this was obviously written yesterday. But I think today's discussion and the model we voted on really points in the direction B

MS. CARR: Should we take that off? Delete that third bullet?

DR. BURKE: Yes, I think we should. I think it is a distraction now. It seems to me there is a discussion between Data Team and Rare Diseases Team about defining rare diseases and that discussion should interact with the test of the model.

MS. CARR: Suzanne, maybe you could just strike it out rather than erase it.

DR. MC CABE: Other issues there? Certainly we had talked about the prenatal issues. That needs to be considered, the technical assistance and rare disease groups, how they could become a part of it. But one of the main priorities will be to look at the model and see how it impacts on rare diseases.

The next group, the Access Working Group--continue defining reimbursement issues, further discuss developing minimum and ideal genetic benefits packages to be used as models for insurers--is that something we want as a priority at this

time? Continue defining health care disparities. Issues in genetics, provide comments on Healthy People 2010 from a genetics perspective. Expand outreach efforts to include others in discussion on health care disparities. I assume that the one on Healthy People 2010 came up at lunch today? How big of an effort is that?

DR. PURYEAR: I think it is a big effort and I am not sure it should be delegated to a work group. Just for a point of information, the suggestion about a minimum ideal genetics benefit package was at the suggestion of HCFA.

DR. MC CABE: I can understand where that came from. I would suggest that Healthy People 2010 be not a short-term priority because that is a major undertaking and we would have to look at that either to be a commissioned effort. I think it would be hard for the members of this Committee to take on. Does anybody on the committee who remains disagree?

DR. KOENIG: My only concern, since Reed has gone, we did have some discussion about how the race/ethnicity and definition issues crosscut the goals of Healthy People 2010 and thinking about differences. That was different.

DR. MC CABE: That would come up in the disparities issue.

DR. KOENIG: I just did not want it to get lost.

DR. MC CABE: Then informed consent IRB--this would be building on the work data team, develop the checklist, develop recommendations for considerations by full Committee regarding informed consent challenges, building on work of others, explore issues of disclosure of research results -- that all came up from this afternoon. Is there anything below the line there? Those were all things we discussed this afternoon. So do you feel comfortable with that, Barbara?

DR. KOENIG: I am slightly uncomfortable with the central IRB issues that are being added quickly without a lot of discussion. But if there is agreement that it is not B

DR. MC CABE: We probably won't get to it until February. You could begin to explore it but focus on the other things. The other thing, I thought that Reed's discussion yesterday about concepts of race, concepts of ancestry, ethnicity were very important. We have talked around them before. We have not really talked about them as openly. They are going to be key to risk analysis in the future. So I have asked that Reed and Barbara get a new group to look at these issues, as co-chairs, and we will be asking others to participate on this. Sarah was asking me where it comes in in the priorities--I think it is a new group and we should develop the group and have them address that. It will be a different group. It will move people into some new activities.

MR. HILLBACK: I was wondering, with David and Steve both here, if we could ask that they try to come back in February with some idea of what their regulatory schema was going to look like. It would not be final or anything else, but I think, given the struggle we have had in relating it would seem to me to be good timing.

DR. COLLINS: Can I strongly associate myself with the remarks of the gentleman from wherever you are from, because I think the central mission of this advisory committee will remain the identification of this particular algorithm and an assessment of how it actually works in practice. I think we are really ready now to hear a drilled down version of that ASAP.

DR. BURKE: I want to third that. I think there is a certain point at which we cannot go much farther with test classification until we know what the level of review

is going to be like.

DR. MC CABE: One of the things I know, Wylie, that you and Muin have been talking about are checklists. I would suggest that you engage them because they have been talking about this a lot and they may be able to help you.

DR. CHARACHE: I am saying the same thing. I think we went through the very nice checklist that Wylie had made for level two that their group come forward with suggestions for level one where they are disparate, as opposed to just quantitative.

DR. PURYEAR: Sarah, can you ask the Department to report on their regulatory or oversight paradigm that is supposed to be developed between CDC, HCFA, and FDA also in February?

MS. CARR: I think our expectation right now is that will be something to report by the end of the year. I think if FDA can report to us, I think that will be--I am sure they will get a sense from the Department.

DR. FEIGAL: It would be useful to see all of it together, though. I think we should encourage the process along to make sure we get -

DR. MC CABE: At least a status report.

DR. KOENIG: I am concerned that two issues which could have been spread throughout all of the groups have now sort of fallen off the radar screen. One is something that Dr. Feigal just mentioned. It is this issue of direct-to-consumer marketing issue which, although I now understand even in greater detail the complexity involved, I really don't want that--maybe it can be back in the informed consent group in terms--it is. Is it still there? I just didn't see it. Forget that. Strike that.

The second one is, just so people understood why I abstained from the

classification scheme, I like it as it is, but I just have not had time to discuss the issue of where we are now on record with the Secretary as saying that we want to use social categories as a way of evaluating tests. And they have fallen off here, so I just want some understanding of this. I still want that to remain on the radar screen in terms of defining them and operationalizing them.

DR. BURKE: Quick comment on that. I think we have already operationalized one in terms of population screening. That is a social issue. I would like to go on record saying that the discussions that we have had about what social issues might constitute ought to be part of and incorporated into the level two review.

DR. MC CABE: The other thing I would ask of the work groups is to develop time lines. Not all of this is doable, but to come back at the next meeting in February with time lines. I hope that you will take those that you identified as the highest priority and Sarah and her staff can help with that, reviewing the tapes. But we want to definitely have some work products, but then develop time lines for the remaining issues that are up here.

I want to thank everybody for a very intensive and productive meeting. Our next meeting is February 15th-16th. Please have a safe trip home and everybody have an enjoyable holiday.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)