CENTERS FOR MEDICARE AND MEDICAID SERVICES

MEDICARE EVIDENCE DEVELOPMENT AND COVERAGE ADVISORY COMMITTEE

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IN RE: SCREENING GENETIC TESTS :
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Wednesday, May 6, 2009

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P R O C E E D I N G S

MS. ELLIS: Good morning, everybody. We're about to start the meeting for today. First we will have words from Dr. Barry Straube.

DR. STRAUBE: Good morning, I'm Barry Straube. I'm the CMS chief medical officer and director of the office of clinical standards and quality, part of the Coverage and Analysis Group who's putting on this MEDCAC meeting today as part of the office of clinical standards and quality (unintelligible) underlying portfolio of oversight from the management side.

I want to welcome this MEDCAC panel. It's an illustrious group of folks, and I appreciate all of you agreeing to be on this panel.

I would like to take a minute or two to set the context. I'd also like to welcome everybody in the audience. You represent diverse organizations. We welcome your input and comments during the open

mike periods.

I also, before we started, for those of you

who've been on the MEDCAC and sat on some of these panels before, you know that Dr. Stephen Phurrough had been the director of the Coverage and Analysis Group. When Steve was here, Steve kept reminding me for a total of seven-plus years, which he said was the longest he was in any one place at any one time. But as you probably know, Steve decided to simplify his life a little bit, and he has taken a position as medical officer over at the Agency for Healthcare Research and Quality and will be working on some comparative effectiveness projects.

I wanted to mention Steve's name before we started, because he has been so integral to the development of coverage policies and basic principles on some rather innovative new directions we've taken over the last several years. So I suspect we'll be seeing Steve here from time to time, but I did want to acknowledge his leadership.

We are -- we do have a posting right now for

that position. It's a very, very important position

in the context of what's going on in health care right

now, so insofar as the panel, the audience, or anyone who know people who might be suited for that position, you're welcome (unintelligible) to go to our website (unintelligible.)

I'd also like to acknowledge that we have a new chair and co-chair of MEDCAC, who, I guess, will officially be in July or June assuming their roles. One is Dr. (unintelligible) who will be chair of MEDCAC. We have with us this morning, who is the acting chair for the moment and will be the co-chair is Dr. Satyi Satya-Murti, who will be chairing today's MEDCAC Meeting.

(Whereupon, there were technical difficulties with the audio.)

About a year and a half ago, I sat down with a coverage group, and we decided that we really needed to try to get ahead of the game or get caught up, frankly, with where genetics were going. So we've been doing some internal work. We've been working

very closely with the secretary's advisory committee

on genetic health in society and decided mid-last

year that we needed to do some MEDCAC meetings on the issue of genetics and genetic testing. So we had, as you know, a panel that met in February looking at the issue of Warfarin testing -- Warfarin genetic testing to determine whether or not those tests were helpful in the management of patients who were being treated with Warfarin therapy.

As you know, that panel came out with a variety of recommendations. But the final, most important piece was that the evidence was not quite there that the panel would recommend that we should cover that particular test without restriction. But at the same time, there was sufficient evidence that it might have some benefit. So we invoked the coverage with evidence development option that we have in national coverage decisions.

And just Monday of this week, we announced the proposed decision for genetic testing with Warfarin therapy, which we're proposing we will cover,

but only under the conditions of coverage with evidence development. So that's the first toe-in-the-

water that we at CMS have taken on this. There's been lots and lots and lots of interest, and we're anxious to see what the comment period will bring for the Warfarin testing issue.

But it's time to keep moving forward, and that's the context of today. And I think it's very relevant, in that President Obama has a large number of priorities that he wants to embark on. But in the health care world in particular, we do know that his priorities include increasing accessibility to medical care and to tests when relevant, increasing affordability of the general health care system, and then finally invoking both personalized medicine, but population health at the same time.

And although one might think that the two are in conflict, I think they are complementary, that is, we need to assure that our general population is taken care of from a population-base perspective, that as many people as possible need to have access to

services that are important and necessary for them.

But at the same time, we're all individuals, and we

have to take into account that special uniqueness that each and every one of us as patients may have.

So the personalized medicine has to balance, I think, with population health. So today Dr. Marcel Salive, who is one of our division directors in the coverage and analysis group, will be representing us here and steering things from the CMS side. And I thank Marcel for doing this. And I thank again all of you as we get into the topic of the day, which again, will be trying to give us some structure on screening genetic tests and what considerations we should take into account as we go forward developing policy on how to deal with screening genetic tests.

So thank you very much. I do have to scoot pretty quickly. I'm going to stay for a few minutes, but I have to get down to D.C. for a meeting with the department down there later this morning. But you're in good hands with Marcel and all of our staff. And again, I thank you in advance for your work here.

Thank you.

MS. ELLIS: Good morning, and welcome acting

committee chairperson, members, and guests. I am Maria Ellis, the Executive Secretary for the Medicare Evidence Development and Coverage Advisory Committee, MEDCAC. The committee is here today to discuss the evidence, hear presentations and public comment, and make recommendations concerning the requirements for evidence to determine if the use of screening genetic testing of beneficiaries without signs or symptoms of disease improves health outcomes in Medicare beneficiaries.

The meeting will discuss the various kinds of evidence that are useful to support requests for Medicare coverage in this field. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers

financial interests. Each member will be asked to disclose any financial conflicts of interest during

their introduction. We ask in the interest of fairness, that all persons making statements or presentations also disclose any current or previous financial involvement in a company that manufactures or provides devices or other tools for the research of screening genetic tests. This includes direct financial investments, consulting fees, and significant institutional support.

If you haven't already received a disclosure statement, they are available on the table outside this room and should be submitted before you make your presentation.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today in a very tight agenda and, therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there

is a chair for the next speaker, and please proceed to that chair when it is your turn.

We ask that all speakers addressing the panel please speak directly into the mic and state your name as this is being recorded. For the record, voting members present for today's meeting are Dr. Marion Danis, Nancy Davenport-Ennis, Dr. Mark Grant, Dr. Daniel Hayes, Dr. E. Craig Henderson, Dr. James Puklin, Randal Richner, Dr. Maren Scheuner, Teresa Schroeder, Dr. John Spertus, Dr. Steven Teutsch, and Dr. Jonathan Weiner.

A quorum is present, and no one has been recused because of conflicts of interest. The entire panel including non-voting members will participate in the voting. The voting scores will be available on our web site following the meeting. Two averages will be calculated. One for voting members and one for the entire panel. I ask that all panel members please speak directly into the mics, and you may have to move the mics since we may have to share.

If you require a taxicab, there's a sign-up

sheet at the desk outside the auditorium. Please

submit your request during the lunch break. Please

remember to discard your trash in the trash cans located outside of this room. And lastly, all CMS guests attending today's MEDCAC meeting are only permitted in the following areas of the CMS single site. They are the main lobby, the auditorium, the lower level lobby, and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now I would like to turn the meeting over to Dr. Marcel Salive.

DR. SALIVE: Good morning everyone. I want to echo my thanks to the panel for your willingness to serve and echo the comments of Dr. Straube. One point, I wanted to thank the panel. Many of you served on the earlier February 25th panel on diagnostic genetic tests. And this meeting as was mentioned will be covered

-- will be discussing screening genetic tests.

So I wanted to just remind everyone of our CMS regulatory, if you will, definition of diagnostic

tests, which are just that the procedure, the diagnostic procedure or test is to obtain information to aid in the assessment of the medical condition or diagnosis of disease. So we contrast that with screening of a person who is essentially healthy or not exhibiting any symptoms of a disease of interest.

I don't have any additional comments at this time, but I'll be happy to interchange with the panel or answer any questions as the CMS representative. And I want to turn it over to Dr. Satya-Murti.

DR. SATYA-MURTI: Maria, as in the past, you want us to introduce a statement of conflict of interest, or is that not necessary anymore?

MS. ELLIS: Yes. You can do that.

DR. SATYA-MURTI: We are --

MS. ELLIS: Yes.

DR. SATYA-MURTI: I'm Saty Satya-Murti. I'm a neurologist with clinical and academic background, and I've been a Medicare medical director for a little

over ten years. And I do some consulting now and do some non-profit and educational and clinical work. I

have no conflicts of interest.

DR. DANIS: Hello, I'm Marion Danis. I'm an internist and a bioethicist. I run the ethics consultation service at the clinical center at the National Institutes of Health and run the section on ethics and health policy. And I have no conflicts of interest.

MS. DAVENPORT-ENNIS: And I am Nancy Davenport-Ennis. My organization is a patient advocate foundation. And I have no conflicts of interest.

MR. GRANT: And I'm Mark Grant. My background is a geriatrician, epidemiologist. I'm an associate director at the Technology Evaluation Center of Blue Cross/Blue Shield Association. I have no conflicts of interest.

DR. HAYES: I'm Dan Hayes. I'm a breast cancer medical oncologist at the University of Michigan with a special research interest in tumor

markers. I have research funding from Pfizer, Novartis, Astra Zeneca, and, in particular, from

Varidex, which is the diagnostic branch of J and J. And one could argue that they make genetic tests, but not in the context I think we're going to discuss today. So I don't think I have a conflict there.

MR. HENDERSON: I'm Craig Henderson. I'm medical oncologist, University of California San Francisco. And I have no conflict of interest.

MR. PUKLIN: I'm Jim Puklin. I am a professor of ophthalmology at Wayne State University, and I'm also chairman of the Wayne State University Human Investigation Committee. And I have no conflict of interest.

MS. RICHNER: I'm Randal Richner. I'm a nurse, a private consultant, have been working for many years in health technology and health economics assessments, and I have one editorial comment to make. I have been on MCAC since its inception in 1999, other than a two-year hiatus, and this is the first time in ten years that I've been allowed to vote. So I'm

very, very happy about this. So I'm going to make my vote count. And also I wanted to say that this also

might be my last time on MCAC today 'cause my term is over. So I just -- I'm very excited to be here, and I get to vote. And I have no conflicts.

DR. SCHEUNER: I'm Maren Scheuner. I'm a clinical geneticist, also trained in internal medicine. I work at the Rand Corporation, where I do primarily health services and health policy research, and also work at the V.A. in greater Los Angeles, where I'm doing health services research. And I am an adjunct associate professor in the department of Health Services at UCLA School of Public Health.

MS. SCHROEDER: I'm Teresa Schroeder, director of clinical affairs for musculo-skeletal clinical regulatory advisors. I'm here as a patient advocate. And I have no financial conflict.

DR. SCHEUNER: I have no financial conflict.

DR. SPERTUS: My name is John Spertus. I'm a cardiologist at the Mid-America Heart Institute and a professor of medicine at the University of Missouri,

Kansas City. I do health services and outcomes research, particularly patient-centered outcomes

research, and I've been very involved in quality assessment and quality improvement. I have a lot of research funding from a broad range of pharmaceutical and device companies. But as it relates to genetic testing, particularly in screening disease, I've done some research, but have no conflict of interest.

DR. TEUTSCH: I'm Steve Teutsch. I'm the chief science officer for the Los Angeles County Department of Public Health. I'm recently retired from Merck, but I have no specific conflicts of interest of a financial sort.

MR. WEINER: I'm Jonathan Weiner from the Johns Hopkins Bloomberg School of Public Health here in town and also the School of Medicine at Johns Hopkins and professor of health policy and management focus on outcomes and health services research. I have no direct conflict of interest, although I'm sure somewhere at Johns Hopkins, there might be some. But that's indirect.

MS. PERFETTO: I'm Eleanor Perfetto. I'm director of reimbursement and regulatory affairs with

Pfizer, and I am aware that Pfizer does own some interest in some companies that may be developing these kinds of tests, but it is not part of my job, and I couldn't even tell you what the names of those companies are. So I believe I don't have any conflicts.

MR. GUTMAN: Hi, I'm Steve Gutman. I'm a guest. I'm a professor of pathology at the University of Central Florida, and I am starting to do consulting through their practice plan. But at this time, no conflicts of interest.

DR. HOLTZMAN: I'm Neil Holtzman. I'm an emeritus professor of pediatrics, health policy, and epidemiology at Johns Hopkins. And I ran a unit called Genetics in Public Policy Studies there, and I also chaired an NIHDOE task force on genetic testing, which was really the forerunner of the secretary's advisory committee. We recommended the secretary's advisory committee. And the monograph, which is

20 available on the web, established, for the first time

21 I believe, analytical validity, clinical validity,

clinical utility, and ethical issues as the major characteristics that should be considered in developing genetic tests. And I have no conflict of interest.

MS. MANSFIELD: I'm Liz Mansfield. I'm the senior genomics and personalized medicine advisor to the chief science officer at FDA in the office of the commissioner. And I have no conflicts of interest.

DR. SATYA-MURTI: Ms. Sandra Jones, would you start the presentation?

MS. JONES: Good morning, and welcome to the Centers for Medicare and Medicaid Services. Today's MEDCAC topic is screening genetic tests. I'm Sandra Jones, a nurse and analyst within the coverage group. We invite you to share in today's MEDCAC. I will present the questions and discussion section that are in the context of screening genetic tests for the early detection of disease.

First, consider are there differences in the desirable characteristics of evidence about screening

genetic tests, versus those of screening tests in general. Then discuss.

Next, consider and discuss what are the desirable characteristics of evidence for determining the analytical validity of screening genetic tests.

Question three part A, beyond aspects of analytical validity, are there meaningful differences in the desirable and/or necessary characteristics of evidence about the affect of genetic testing on outcomes? If yes, please consider question three separately for each of the paradigms.

Question three part A, the testing paradigms are one, early detection of disease in an asymptomatic person, and two, early treatment of disease before signs and symptoms are apparent.

Question three part B, what comparative data are needed on alternative strategies for screening?

Question four, for each type of outcome on the next slide, how confident are you that the

methodologically rigorous evidence on the outcome is

sufficient to infer whether or not screening genetic

testing is effective for the prevention or early detection of illness or disability?

Question four, rating types of outcomes. For each lettered outcome, assign a number from one to five to indicate your vote. A lower number indicates lower confidence. A higher number indicates higher confidence. The outcomes are A, additional confirmatory diagnostic procedure; B, survival and other; and C, other patient-focused health care outcomes such as functional status and incidence of adverse events.

Question five, what are the desirable measures of the cost effectiveness of screening genetic tests for the prevention or early detection of illness or disability?

Question five continued, consider ranking one equals the lowest and three equals the highest for the below A through C options and/or identify other measures that would be appropriate; A, quality-

adjusted life years gained due to screening; B,

decreases in incidences of illness or disability or

net gains in other patient health care outcomes; C, net changes in lifetime costs of illness or disability, and then discuss.

Question six, what are the desirable methodological characteristics of studies of cost-effectiveness for screening genetic tests for the prevention or early detection of illness or disability? And then discuss.

Question seven, are there ethical issues particular to screening genetic testing that may alter the methodological rigor of the studies of genetic testing? Then please discuss.

Question eight, does the age of the Medicare beneficiary population present particular challenges that may compromise the generation and/or interpretation of evidence regarding genetic testing? Then discuss.

On behalf of our coverage team, thank you for your attention and participation in today's MEDCAC

and your patience with not being on the proper screen.

Next, Dr. Jeffrey Roche.

DR. ROCHE: Good morning everyone. Thank you for coming to CMS today to discuss screening genetic tests and especially the kinds of evidence that CMS should be looking at in determining coverage for such tests. My very brief presentation will discuss only a small amount of background information that may be of help to you as you consider these questions.

A screening test is, very simply, a test to detect a disease before it becomes symptomatically apparent or before it demonstrates signs of its presence. Under Medicare Part B, screening tests are covered in order to provide disease prevention or early detection services to Medicare beneficiaries. In some situations, as everyone probably knows, the advantages of screening tests are very clear. For example, the early detection of various types of diseases such as cancers can lead to far more effective treatment and far better survival.

It is known also that there is evidence about the effectiveness of screening tests. For

example, in breast cancer screening, it is known that there is a significant reduction in the deaths due to breast cancer due to screening programs involving mammography. However, there is also evidence that some types of screening have not proven to be as effective in preventing or decreasing the number of deaths. For example, using different types of screening techniques to decrease lung cancer deaths.

Over the years, guidelines which have been developed choose the appropriate screening tests for their patients have been revised as more evidence of their effectiveness and the age groups at which they are effective becomes available.

Now, among the many advantages of screening, certainly more efficient and less risky treatment as well as the prevention of loss of years of life and the contributions of individuals are major advantages. However, screening is not without some disadvantages. There are risks to the person who has been screened.

There may be risks in terms of the amount of resources

that must be committed for the screening of a

substantial portion of the population.

Now, as I mentioned before, Medicare already covers a number of screening tests. Some of these are shown on the screen. And, as you can see, not all of them are laboratory tests. Some are imaging procedures, some are special clinical examinations such as sigmoidoscopy. But recently, due to the enactment of what's call the Medicare Improvements For Patients And Providers Act of 2008, a particular section, section 101, authorizes the Secretary of Health and Human Services to consider additional preventive services benefits under Medicare, if certain conditions are met.

In particular, MIPPA 101 suggests that those conditions are the following: a newly proposed benefit that provides preventive services must be reasonable and necessary for prevention or early detection of an illness or disability. It must be recommended by the U.S. Preventive Services Task

Force, with either a grade A or grade B

recommendation, and it must be appropriate for persons

eligible for Medicare parts A or B. In addition, it must be considered within the framework of the National Coverage Determination Process. And finally, section 101 authorizes the secretary to assess the relationship between the predicted outcomes and the expenditures for such preventive service and may take into account this relationship in making a determination about its coverage under Medicare.

Now, for other NCD processes, as you probably know, evidence plays a large role in what we do at CMS. And this will also be true for any future considerations we may do of genetic tests that are being used for screening purposes.

In particular, we will be looking for evidence concerning benefit and especially net benefit. That is, the degree, extent, or amount to which a screening service accomplishes good, in contrast to the harm or harms it may be associated with.

A number of authors have suggested that there are particular needs for stringency in examining

evidence about screening tests. For example, on this slide, some well-known authors in the area of clinical epidemiology have suggested that a well-conducted randomized control trial is the best design for a clinical study, which minimizes bias in considering the benefits of screening tests. In fact, these authors have proposed several designs, which may prove useful in such clinical studies.

In addition to the other sources of evidence, on a conceptual level we actually have seen some large-scale trials reporting recently, on at least their preliminary experience, as far as the efficacy of screening testing. And some of these, as you will see, are not based specifically on genetic testing, but on other types of screening. For example, the use of prostate specific antigen screening for the detection of prostate cancer.

This article, for example, which was published about a couple of months ago, showed that

after seven to ten years of post screening follow-up,

there was no significant difference in the number of

prostate cancer deaths in the screening group as opposed to the control group.

A second study, which was done in a somewhat different manner, but involved a great many more participants and also had a longer follow-up period, showed that there was a protective effect of PSA screening, especially in the screening group, which becomes apparent only after ten years of follow-up post screening.

The authors of this study concluded that PSA-based screening for prostate cancer was associated with a 20 percent reduction in deaths from prostate cancer. There were a variety of sources of other evidence about screening and its effectiveness. We are indebted to our colleagues at the Agency for Healthcare Research and Quality for the many technology assessments and other studies they have done on this area, especially in the area of cost-effectiveness.

Other groups, of which we'll hear more from later speakers, including the EGAPP working group at

CDC and the U.S. Preventive Services Task Force, have published reviews of evidence about screening tests and recommendation about their use in clinical circumstances.

Finally, CMS is very aware that with the onslaught of information about genetic conditions that may lead to serious diseases that may afflict Medicare beneficiaries, it is important for us to continue to be aware of new developments that may provide benefits for our beneficiaries.

For example, screening for certain alleles of the gene may provide information on the relative risk of Alzheimer's disease. Based on your discussions and recommendations today, CMS will evaluate the evidence on such screening tests and will determine whether genetic tests used for screening purposes are appropriate for Medicare coverage.

Thank you again.

DR. SATYA-MURTI: Dr. Feero, you're next.

It will be good to have the next speaker waiting

towards the end of the previous speaker to save us a

little ambulatory time.

DR. FEERO: I need my slides, however, so I got a little scared this morning when I handed in my thumb drive, and they said, "We can't take that." And I said, "Uh-huh, I'll wave my hands." And it turns out that what I sent them in on Monday they already had them loaded, which is great.

So, I really want to thank all of you for the opportunity to come before you today. You know, in terms of conflict, I have to say that, in fact, I'm inherently conflicted, I guess, because I work at the National Human Genome Research Institute. And it tends to be that my boss thinks that genetics might actually be useful ultimately in health care. But in terms of actual financial conflicts, I obviously have none.

And the fair number of slides I'm going to go through this morning for you -- I want to say that I think my presentation you're going to find is

probably a foundation for your discussion today. If you remember sort of one point before you leave --

from my talk today, it's the idea that you have to be able to walk before you can run. And that's why I'm going to give you an update on family history.

So, genetics is clearly in the air right now. You can't hardly pick up a major media outlet and not find a story. And in the last week, there have been a number of things on CNN, New York Times, just a vast barrage of new findings. And there's a good reason for this; because in the last few years, a type of study called the genome-wide association study has really broken open the genetics of complex common conditions.

And prior to about 2005, most genetics and genomics was really restricted to understanding of single-gene disorders. And really, we've made great inroads into the things that really matter most in terms of public health impact: heart disease, diabetes, stroke, Alzheimers, et cetera, et cetera.

And this slide summarizes the number of

conditions for which there are now robust, disease

gene associations since 2005. And it's really, really

remarkable. It's literally a tidal wave of new discovery. And on this list you'll see things here that probably account for the top ten causes of death in the United States aside from things like trauma, et cetera, et cetera.

And this wealth of new discovery has led a number of organizations to try to move this information into the health care arena through so-called genome-wide scans, where essentially you can purchase for a relatively low price a measurement of a number of these genetic markers, literally thousands across your genome. And the companies will provide information that purportedly tells you a little bit about your risk for common complex diseases.

And this has obviously caught media attention. Time's best invention of the year in 2008, was the retail DNA test. However, there's a lot of controversy surrounding the use of these types of tests in this way at this point in time. And I think,

the vast majority in the scientific community feels

that this type of testing at this point is really

premature for use in mainstream medical care.

This title doesn't quite get it right with the New York Times, but it's discussing a series of New England Journal articles that really point out the fact that as of right now, although these disease gene associations are robust, they, in fact, predict only a limited amount of the inheritability of conditions such as type 2 diabetes. And we really need to learn more about what those other genetic factors are to gain a better picture of how to use this in health care.

So, all kinds of questions should be floating about in your mind with regard to genetic tests in mainstream health care. And for the genome-wide scans, particularly, these come to the fore.

I'm going to try to convince you this morning that family history is still the cheapest, most accessible, most time-tested way to get a rough estimate of the genetic component of disease risk.

And it's not going to go away in terms of its importance.

If you look at the top ten causes of death in the United States, in red you'll see things that family history clearly plays a role in helping to predict risk. And you could argue that, in fact, influenza and pneumonia and septicemia are also influenced by familial factors. And we don't understand those quite as well as perhaps some of the others.

The public, in general, recognizes the value of family history. In terms of health, this is some very recent data from Oregon that shows that of the folks that they surveyed, 99 percent agree that family history is important to their health and up to two-thirds have collected some family history information -- about two-thirds relative to their health and family history.

So aside from the use of family history and risk assessment, family history has a rich tradition in health care of providing other useful bits of

information. It helps you understand family

structures, relationships. It helps you learn about

patient concerns.

I think as clinicians, most of us have the experience of a, you know, 40-year-old male, who's otherwise healthy, coming into your office for their physical. It's either their wife sent them in, or my brother just got diagnosed with X, Y, Z. It helps to inform differential diagnosis, case finding, and finally risk assessment.

I would argue that as we think about the medical home, family history clearly has to be a foundational piece of that medical home model in reforming health care.

Family history is also fairly well accepted in terms of a genetic test by the medical community. If you look at the continuum and the type of tests that are out there, I think most clinicians would not argue with you that family history is a fairly well accepted part of the armamentarium.

And the risks conferred by family history

are actually pretty substantial. In comparison to,

say, a single nucleotide polymorphism associated with

a common complex disease, a single first-degree relative confers these types of elevations in risk. And that's just a single first-degree relative.

In families that have, perhaps, more single-gene-based risk for complex disorders like colorectal cancer, the risks may be vastly higher than that, if there's the correct pattern of inheritance in the family.

Another rap against family history has been the sort of sensitivity and specificity of patient-provided information. I think in the last few years, you've seen some reports out of AHRQ looking at the evidence about this. And it's actually not too bad. The sensitivities and specificities for four selected cancers, looking across all relatives in families in the studies that they were able to look at, you see they're comparable to many of the screening tests we consider part of routine care at this point in time.

Additionally, there are a variety of

clinical guidelines that utilize family history information. In fact, they're integral, and we'll get

back to the USPSTF in a while. And clinicians obviously have to react to these guidelines.

Despite that, family history collection is actually quite poor by primary care clinicians. And I would argue that it's going to get worse, with the advent of electronic health records, as most systems are not well set up to enable clinicians to collect family health information.

So what are some possible keys to increase utilization of family history in our health care system? One is to work on improving the evidence base and education of clinicians and the public regarding family history. And there have been a number of activities ongoing on the federal level, state level, and private sector to do so.

This is just an example of family health where a trial at the CDC has recently conducted -- where they used an electronic web-based family history tool to provide risk assessment, deployed in a

population essentially to look to see if they could see any changes in outcomes.

The information -- this is very preliminary, this slide -- and I'm sure it will probably be in your packet. Very preliminary, but it's promising. The papers are going to be rolling out in the next several months to a year with regard to this trial.

Later on this summer, the NIH is sponsoring a State of the Science Conference to try to bring together a broad picture of what we know about the use of family history as a screening tool in medical practice, particularly in the primary care setting. That's slated for August 24th to the 26th, 2009.

It's a public meeting. You're all welcome to attend. There's a very, very large AHRQ literature review that goes into this, as well as 21 speakers that will be presenting on family history information.

So the key questions are things that I think you'll find are important to what you're considering today. What are the key elements in a primary care setting of a family history, the necessary for risk

assessment purposes. And I won't go through these slides in any detail. Again, they're in your packet.

That's why I put in a lot of slides to give you the information.

But I think they're going to be -- the conference will address a lot of questions that are really key for you determining the usefulness of family history in primary care as a screening tool.

So next step: remove barriers to collection. Well, there are a variety of reasons why family history isn't collected. But I think they all relate back to time and money.

Collecting a good family history is actually probably more time-consuming than most primary care clinicians are willing to invest. In the context of an office visit, the general average is, you know, seven to ten minutes. And it takes a good 20 minutes to collect a good family history.

So the U.S. Surgeon General's office in recognition of this has been working over the last several years to develop sort of alternative ways to

get family history information into the health care system. And one of these is through the development

of the surgeon general's My Family Health Portrait Family History tool, which essentially is a patient-interfacing, web-based, family history tool that allows an individual, sort of, in the context of their home environment, when they're relaxed, they're not thinking about 14 other things in the doctor's office, to complete their family history and then communicate that to their health care provider.

In the recent past that tool is updated, so that it now offers connectivity to PHR and EHR systems. And I think this will be a major advance. In the past, the tool was sort of a stand-alone entity. The individual that used it to complete their family history was essentially forced to print it out and then hand-carry it to their doctor.

The tool is now available to be embedded behind fire walls, for example, in a PHR system, and to be seamlessly connected to the EHR system.

So other barriers -- concerns about genetic

discriminations. Two thousand eight was a landmark year. It saw the passage of the Genetic Information

Non-Discrimination Act, which prohibits the use of genetic test information including family history in pre-symptomatic individuals for discrimination in the setting of employment or health insurance. So that barrier has, at least, been reduced. I'll admit it's not entirely removed as an issue, but it's been reduced.

Additionally, there have been concerns about the use of family history and how HIPPA rules would be viewed with this. This year there was actually -- yes, it was this year. Two thousand nine, OCR, the Office of Civil Rights, put out some guidance on the use of family history tools, such as the family health portrait tool of the surgeon general, which strongly suggests that family history information is not inherently different than other types of personally identified information.

In fact, you can as a patient provide your doctor with your relatives' family history

information, their names, et cetera, and doctors can

share that information as they would, under the same

sort of rules they would any other bit of your health care information.

So help with interpretation. Well, the next step for the surgeon general's tool is to throw a rock in the pond around developing clinical decision support tools that can operate off of a web-based method for collecting family history from patients.

So right now, the CDC, the National Cancer Institute, the National Human Genome Research Institute, and the Office of the Surgeon General are partnering to look at taking colorectal cancer as a model, developing some appropriate risk algorithms to apply to family history information, and then building essentially an electronic tool to enable health care providers as well as patients to better understand their familial risk at the point of use with such tools as the My Family Health Portrait tool.

So I spoke really quickly to get to this point, value in collection. This is, I think, a

fundamental issue with regard to family history

information and the fact that our health care system

is so time conscious at this point and, in general, in the primary care setting, operating with narrow margins, in terms of their ability to recuperate costs for doing something extra.

So is this a possible role for CMS? One, you could think that CMS would be able to incentivize collection of structured inter-operable family history information, like that collected by the surgeon general tool. By all means, it doesn't have to be collected by that tool, but information that can be imported into say an electronic health record and moved around effectively as a patient moves from provider to provider.

This could be done through PQRI. And I know this is a huge hurdle, but possibly a new code for collection of complete, whatever that means. And I think that's a point for debate of family history information.

I think traditionally CMS to me has seemed

fairly conflicted on this issue. And looking at what

Dr. Straube said at SACGHS in March, I think you can

see that in his slides. You found the following two statements. For example, Medicare does not cover genetic tests based on family history alone. And I would challenge you to say that in the year 2009, that you may need to rethink this versus this new issue that's come up with MIPPA, about considering preventive services that either get an A or B rating from USPSTF.

Well, let's take a look at USPSTF guidelines. Overtly, family history is mentioned as important in the consideration of breast cancer screening. Somewhat less overtly it's mentioned in the lipid screening recommendations, where family history is considered one of the cardinal risk factors for starting screening early for hyperlipidemia.

It's mentioned in the colorectal cancer screening guidelines, in that you can't apply the A guideline unless you know the family history because those folks that are at risk because of elevated -- of

20 a familial pattern of colorectal cancer should be

21 starting screening earlier than these guidelines

recommend.

For triple A screening, it's also buried in the guidelines, that family history is a consideration for screening for that. And then for a whole host of other disorders, some like newborn hearing screening aren't terribly relevant to Medicare, but family history is clearly an integral part of what USPSTF guidelines have to say.

And I want to point out to you that, in fact, you cannot use the USPSTF guidelines unless you have family history as a foundation because there are caveats to many of the guidelines that say, you know, if there's a family history of X and such, then this guideline does or does not apply.

So other things CMS could be involved in. There are a number of demonstration projects ongoing around the country with CMS working with personalized health record-type systems. It would be, I think, a fairly easy slam dunk to incorporate some family

history tools into those demonstration projects and to see what public acceptance is, what utilization is

like, how does that information migrate to health care providers. I think we could really learn a lot and provide direct benefit at the same time.

And again, we have a tool that would be relatively easy to do that with. Again, I have no financial interest. Nobody has any financial interest in this tool. I'm just saying it's there, it's ready, you could use it.

So finally, if CMS could do coverage with evidence determination for widget X, why not for family history tools? And I actually did these slides over the weekend in the Denver airport, so I hadn't known that this Warfarin statement would come out. So I feel a little like I'm repeating something that just was said. But, you know, certainly I think there's opportunities here for doing things with, say, clinical decision support tools that provide risk assessment in a coverage with evidence determination setting that could really advance our understanding of

utility of family history.

And, you know, as with many things in

genetics, we're sort of at the point where we think that there is potential benefit. This is again from one of the AHRQ literature reviews. They came up with a conclusion when they looked at risk assessment tools, that the number of them in develop -- they look like they're promising in preliminary studies, but in the real world, we don't know absolutely what the utility of the risk assessment tools are.

And I would argue that, in fact, well-controlled, randomized controlled trials, we'll never know what the real world utility of these tools are. And I think that's the beauty of coverage with evidence determination.

So, conclusions; family history is really a versatile and potentially powerful tool for improving health care. It's not only relevant to risk assessment for common complex conditions, but it provides a whole host of other functions in medicine that are sort of squishy to try to quantitate, but

they're there and are quite important.

In the long run, family history will not be

supplanted by genetic testing. Family history will always be important to contextualize genetic test results and to help guide their selection. Even with the advent of genome-wide scans and full genome sequencing, we're still going to need to know family history information.

And finally, I think there are numerous opportunities for CMS to advance the use of family history in health care and, ultimately, improve how we deliver health care to the American public.

Thanks.

DR. SATYA-MURTI: Thank you, Dr. Feero. We are somewhat ahead of time. And if there are very focused questions on this particular presentation, we may have a few minutes for that. I do have one I wish to ask you briefly. Thanks for that refreshing re-visit on family history and your middle bullet that it's not so likely to supplant genetic testing.

One concern with Medicare age group

particularly, is one of the reasons of bedside family

history gets de-emphasized is patients are already

symptomatic. So seldom do they need that prior probability force to engage one to go on to test.

So in the Medicare age group, at least family history is important, but they have become symptomatic again. Our purpose today

DR. FEERO: Well, prior to coming to the Genome Institute, and actually while I was at the Genome Institute, my real life is actually as a family physician. And I'll tell you, while I was in practice in Maine, about 60 percent of my patient panel had Medicare. And it's true, many of them did have diagnoses. But a lot of Medicare work actually occurs in the ambulatory setting where family history is important.

And, in fact, I would also argue that family history is frequently used sort of subliminally at least, by health care providers, in the setting of symptomatic individuals to sort of provide again that pretest probability, e.g. the individual who presents

with chest pain in the E.R. of unclear ideology. And

you're sort of sifting through what is the likelihood

that this is due to a cardiac origin.

Somewhere in the back of your mind you're thinking, oh, you know, do they have a family history. And most E.R. docs do ask that question, at least. Wouldn't it be nice if we had that sort of embedded in our health care system so that it didn't get asked -- every time someone went to the E.R., didn't get asked every time? You know, that there was sort of a bedrock of that information that everyone could draw on, much as you'd draw on any allergy list.

DR. DANIS: I'd like to follow up on the last question. I'd like you to say something about whether the primary care setting, where you're taking care of a geriatric patient, is going to be -- whether the care of patients in that setting is going to be better if you're screening for family history or if you're screening for other things in this population, like falls, nutritional deficiency, loneliness, confusion.

I think there are a lot of things that we need to be screening for in this population. And I

worry about the opportunity costs of spending time on a family history when there are so many issues that need to be screened for in this population.

DR. FEERO: I as well. And I'm sure you're familiar with the publications of Yarnell and others that take the USPSTF guidelines and try to apply them to a patient panel of about 2500 and find out that it would take one doc working eight hours a day for an entire year to do that alone, without regard to any of the other considerations for care in that panel.

I can only point out that again, many of those other screening issues are modified by having family history information. So you say screening for depression -- well, in fact, I think if you look, there are probably some recommendations somewhere that utilize family history as part of what you do in this screen.

I would also suggest to you that family history is somewhat more -- although there's clearly

need for updates of family history, somewhat more of a

one-off than say, fall-risk screening, for example,

which really probably ought to be occurring with each of the visits of your geriatric patients.

And so I think there are ways to mitigate this. And also the idea of moving the family history collection somewhat offshore, putting it more -- empowering sort of the patients to do some of the collection for the clinician so that either the clinician or their office staff isn't fully tied up with the basic gathering of the data and further improving how that information is managed. Using electronic clinical decision support tools could mitigate, you know, the impact. But I agree it's an issue, and it has to be considered.

DR. HOLTZMAN: I'm just wondering why we don't consider family history as a screening tool itself, particularly in the context of Medicare, whether if we were to recognize this as something reimbursable, it wouldn't encourage the use of family history to a greater extent than it's used now.

DR. FEERO: That is, in fact, why I put up the idea of a code of collection of a complete family

history. However, as we found out in trying to frame the AHRQ literature review on family history for this family history in improving health conference, it's pretty hard to wrap your brain around the entire spectrum of family history.

You know, I sat down, and talked at some length with Al Berg and others involved in USPSTF, sort of framing their guidelines, and said, so why haven't you guys ever come out and said it makes sense to take a family history? And they said, well, because, you know, it's hard to say that. It makes sense in what context, for what disease? So what they've done is sort of by piecemeal put family history in as being important to a huge number of guidelines.

And I think it's -- that's the way it's evolved. And I guess I would argue we're at the point right now to think about doing exactly what you said, which is to say, look, there are all these USPSTF

guidelines out there that say we should have family history information in order to interpret and use the

guidelines. Maybe we ought to just, you know, bite the bullet and say, this needs to be in there. We need to find a -- this information needs to be in the record. We need to find a way to incentivize it getting there.

DR. HOLTZMAN: You've already got this, what you call, this new interoperable tool for patients to fill out. So obviously, there's a lot that's been done already to try and delimit to some extent family history and still make it a useful tool.

DR. FEERO: Correct. We tried.

DR. SCHEUNER: Thanks, Dr. Feero, that was a very nice presentation. So if you could just answer for me one question. I'm trying to help the panel think about genetic tests for common diseases. Clearly in the Medicare population, which is generally an older population, the complex disorders, multiple genes interacting with each other and environment, family history can represent in large part some of

those genetic factors.

But also you gave an example with BrCA1 and

2 and hereditary non-polyposis colorectal cancer, where family history is instrumental in identifying those individuals in the population who might have a single-gene disorder that's highly penetrant. So it seems to me there are two different roles here for family history. One is possibly to identify these rare, single-gene disorders that are highly penetrant and the other is for the complex disorders.

And as we think about our charge today, I don't know if you could -- maybe should we be thinking about these things in two different ways, or could you comment?

DR. FEERO: Well, I agree there's very much sort of two different ways to approach this. And clearly you would like to find those people with the rare, truly syndromic types of risk for various disorders, whether it's breast cancer or colon cancer, because there's clear-cut evidence that if you can identify those people and get them into proper

screening pathways earlier, that you actually improve

morbidity and mortality for both breast cancer

syndromes and hereditary colorectal cancer syndromes.

The issue there is on a population basis, you're applying sort of a fairly wide-toothed comb to catch something that's pretty uncommon. But I think if you put the two together and say, you know, looking at the more common things and as a by-product, we pick up these rarer things in the process, then it becomes a very reasonable proposition to incorporate that.

I think it might be hard to make a case to say, you know, we're going to design and deploy a tool that only looks for hereditary breast and ovarian cancer syndrome and apply it to an entire population. But if you say that by deploying that tool we might enhance baseline screening rate, mammography screening rates, and even average and slightly elevated risk individuals, then the value proposition for that tool, I think, is much more favorable in terms of its use in populations.

So I would argue for hereditary colorectal

cancer that's particularly the case. If you could use such a tool as a framework for discussing risk

screening for those people who are an average risk or very slightly elevated risk or moderately elevated risk, those folks, say, that have a single first degree relative for colorectal cancer, you might move the needle in terms of screening on a much larger segment of the population.

And so I think it's actually important to recognize that there are two sort of distinct potential roles for family history. But then when you're considering the value, you want to probably try to merge those two things together in your thinking.

DR. SPERTUS: I had just one quick question. I thought it was a terrific presentation. You clearly underscored the importance of family history. And, you know, just conceptually and maybe other colleagues here at Medicare should, you know, explain this to me. It seems like there are two separate themes to this. One is the need to collect the data and, you know, I applaud the efforts to make an inter-operable system.

But with, you know, Google Health and Microsoft Health

Vault and other things, there's a lot where the locus

of responsibility could be with the patient to collect and assimilate it. And that really it's the review of a detailed family history that ought to be endorsed and supported. And whether or not that ought to have a separate code, you know, we don't break apart lots of aspects of the patient/doctor encounter, such as, you know, did I listen to the heart? Yes. I get 35 cents for that. Did I listen to the lungs? I get 75 cents for that. You know, it seems like it's part of a complete visit.

And so I'm struggling because I think it is absolutely essential. It's going to lay the pretext for all of the sort of, you know, appropriate patients that would warrant genetic testing. We'll mandate as a part of that a very thorough review of an accurate family history. But is that a separate Medicare code, or is that just part of good clinical care, and that there ought to be a major public health effort to get the documentation of a thorough family history on an

20 open-source document?

21 DR. FEERO: And I too have struggled in my

thinking on this particular issue. You know, the situation as you and I probably know it at this point in time is when you admit someone to the hospital, all you need to say is family history of diabetes, and you're done. Clearly that's insufficient to drive this type of comprehensive care in a medical center or home.

Family history information, to take a good family history actually takes 20 minutes. It's probably not something that you're going to get many primary care providers to do, when their average physical exam is only about that long let alone an acute-care type of visit.

And family history information gathering at least, unlike, say, the clinical exam could be in some ways distinct from the provision of the office visit service itself. So that if you could find a way to incentivize simply having that information, it would sort of unleash sort of more novel models for

gathering that information than having the, you know,

very valuable health care provider time sort of being

ascribed for asking the questions of the patients.

And I think there's preliminary evidence to show that electronic tools for collecting family history or paper-based tools for that matter, are actually no better or worse than asking the patient face-to-face in a primary care visit if they have a family history of X, Y, or Z .

And so I think given that there is some evidence to suggest equivalency of sort of novel ways to collect it outside of the office visit, the fact that it is a fairly well-circumscribed body of information, and it does take some time and really is foundational, I think argues that it may be worth considering ways to incentivize it distinct from the collection of the history of present illness, which is clearly, you know, something that is immediately of interest to that particular visit.

It's clearly part of -- going to guide the physical exam immediately. It may be important to

long term care that particular history, it might not be. It might be for a sore throat, whereas the family

history information you gather is not only relevant to that visit, it's relevant to the next 20.

DR. SATYA-MURTI: One more comment, and then we'll go onto the next.

DR. SALIVE: As a CMS representative, I just wanted to try to clarify. I think that the focus of this panel is not to discuss whether we should add any new codes to the program. I think it's a provocative point and well taken, and I think is foundational to some of the discussion, and I think has raised some of the key issues for the panel.

But we don't need to dwell on that. I do note that someone in the audience is from CMS who deals with coding issues. So probably it's been heard, and we can move on. But thank you, Dr. Feero, and thank you panel.

DR. SATYA-MURTI: Thank you very much. Yes. It would be a nice day when we get incentivized to do family history. AMA will have a lot more work to do.

Dr. Teutsch is next.

DR. TEUTSCH: Thank you so much. I'm Steve

Teutsch with the Los Angeles County Department of Public Health, and it's a particular pleasure to be speaking to you about something other than influenza today. I've been involved with preventive services for a long time. I was on the U.S. Preventive Services Task Force until recently; was involved with the panel on cost-effectiveness as well. So many of the issues we're talking today are very, very relevant.

I also chaired the secretary's advisory committee on genetics, health and society, which has recommended to CMS that they look into these issues. So we are particularly gratified about the meeting in February and the one here today.

I'm actually here to talk to you about something a little different and that's the work of EGAPP and how EGAPP looks at evaluating genomic tests for screening.

We sort of -- I sort of think about the

translational process as you go from gene discovery

and health application on into practice and then sort

of looking at what the population impacts are as having the evidence-based guideline at the fulcrum. That is, the key part as you move out of the primarily research environment into the primarily care environment. And the question becomes, where do you place that fulcrum, and how high does the evidence bar need to be for different types of applications?

So as one moves that fulcrum to the left so that one introduces technologies earlier, we tend to have less information than we might like on clinical validity. There's frequently no information available on clinical utility. This is likely to lead to lack of coverage because we don't understand these things, that there's the potential for increased harms, but there's also the potential for increased benefits because you get them out there earlier where they can be used.

So the use, in fact, as you move upstream tends to be based on pathophysiologic logic,

pathophysiologic reasoning, expert opinion and so forth. Some people think that moving that bar farther

to the left also stimulates innovation because you can get technologies introduced more quickly. Whether that's true or not, I guess, remains to be seen.

The flip side of that is, if we move that fulcrum farther to the right, we often have much more information about those tests before they get introduced into practice broadly. And that helps understand the validity of the tests, helps us understand the utility better. Clearly if you understand that and they are valid and useful, that provides a basis for better reimbursement.

But it takes longer to get them introduced, which may have the -- disincentivize the developers. The good news on that is, as you move it farther to the right, there's less potential for harms, and there's the flip side, of course, of diminishing the benefits along the way as well.

So partly to begin to address this set of issues across sort of a variety of applications of

genomics, in 2004 CDC convened a panel, which is the

evaluation of genomic applications in practice and

prevention, which was basically to begin to apply evidence-based processes to evaluating genetic tests and other genomic applications.

We are a work group, which is a 13 member, independent, non-federal panel analogous to the U.S. Preventive Services Task Force. That is, it's not really advisory to the government.

We adapted the methods of the U.S. Preventive Services Task Force in many ways. And one of the key things of the U.S. Preventive Services Task Force has been to assess the balance of benefits and harms to assess the net benefits.

And because of the particular issues surrounding use of technologies in asymptomatic populations, we pay particular attention to the potential harms in our assessments. The group has used the ACCE framework that you heard a little bit about from Dr. Holtzman earlier, as a framework for beginning to think about this. And that's one of the

20 differential points with the Preventive Services Task

21 Force, which usually takes analytic validity for

granted.

We conduct systematic reviews of the evidence, and then we make evidence-based recommendations. And I'd like to talk to you a little bit about sort of how that goes -- how we've been doing that.

Basically the work group started by establishing methods and process and then selected topics for review. The task force itself -- the work group itself doesn't generally do the evidence reviews, but we do serve as technical experts for commissioned evidence reviews and try and provide some oversight to the reviews that are actually done.

We then developed conclusions or recommendations based on the evidence, and then provide guidance and feedback on other project activities that relate to dissemination translation and so forth.

Many of you may have seen this publication

earlier this year, which was basically a way to disseminate our methods to this point. This is a

demonstration project, so this is a work in progress. But nonetheless, we try to lay out the methodologies that we have developed today so that they could be reviewed, critiqued and so forth. And those are the methods that we have been applying.

I want to be clear though that EGAPP's looking at a whole variety of application of genomic tests from diagnostics, disease screening, risk assessment, prognosis and predicting treatment responses. So we're looking at a variety of things. Clearly today we're focusing on one aspect of that which relates to screening in an asymptomatic population.

But what I want you to focus on in this particular discussion, is the fact that we've tried to look at what are the standards that should be in place for assessing clinical validity and clinical utility under each of those scenarios.

So for disease screening, we really want to

know about the association of the test result with the disorder. And for clinical utility, we basically look

at improved health outcomes as the sine qua non and the usefulness for clinical decision making.

And I want to point out, this isn't just about getting information. We've had long discussions about what the appropriate outcome should be for assessing the value of these tests. And basically it is to look at the clinical outcomes or the clinical use of these tests and not just for simply generating information that may be useful for people for other reasons.

I'm taking a simple example here because it's easier than the next slide I'm going to show you. And this was one of our initial evaluations, to look at, sit for, 50 testing in adults with non-psychotic depression. And what I want to point out is, that for each of the clinical scenarios and tests that we want to look at, we create an analytic framework, which basically lays out the logic of our thinking and identifies the key questions which are shown here in

numbers that we want to answer.

So really what we'd like to know is the

answer to number one. We'd love to have studies that look at adults with non-psychotic depression who are entering SSRI therapy and get tested. And then we would like to leap all the way to the end and look and see whether they have improved outcomes, which in this case were defined as symptoms of depression, shorter time to response, fewer drug reactions.

As you're well aware, we rarely have studies that look at that overarching question. So what we do is, we then break these questions -- break that down into a series of steps, looking at whether or not the test can properly identify the genotype, which is the analytic validity question, and then categorize the phenotypes to see how that relates to predicted drug efficacy and adverse drug reactions, which are things that we would like to avoid and whether that then affects treatment decisions and whether those treatment decisions then affect the outcomes that we've defined.

So we look for the entire chain of evidence,

and we look at the evidence on several dimensions. We

look at the -- as we do systematic searches, we look at the quality of the individual studies. We look at the quality evidence of each of the linkages and the answers to the questions in general, as well as then whether we have a coherent, consistent body of evidence that allows us to connect all the dots in that pathway.

This is one that's a bit more relevant to screening. It's a bit more complicated because it's related to genomic tests for ovarian cancer and detection and looked at a variety of things beyond just the screening issue. But what I want to point out here without walking you through all of that is to say that we basically construct the same type of logic framework for a series of -- for each of the steps. In this case, all the way from an asymptomatic population of adult women, onto whether we get better morbidity, lower mortality and better quality of life looking at the entire process.

So what we also tried to do is to find the evidentiary standards and sort of what we think is

better or less good evidence for analytic validity, clinical validity, and clinical utility. I'm not going to walk you through all of that here. I want you to see that it exists and basically follows the framework that we talked about earlier.

So we get to prevention. Clearly use of -- this is about use of genomic tests in an otherwise asymptomatic population. And as we look at that, there are characteristics of genomic tests, but they don't, in fact, differ markedly from any other kind of screening test.

We worry a lot that there are a large number of unaffected individuals who may be subject to harms from any type of a screening process. There's usually a modest number of individuals, who are actually identified, who actually have the condition of interest.

These tests need to meet standard screening criteria, which I think most of you are already

20 familiar with. And perhaps most importantly, we want

21 to see that there is an effective intervention to

improve clinically important outcomes. Because at the end of the day, this is about whether or not one can modify outcomes. And we need evidence that one leads directly to another, and there are appropriate actions that can be taken that actually do improve outcomes.

Greg walked you through very nicely a lot of the work of the U.S. Preventive Services Task Force. I think the task force itself thought it was only doing -- assessing genetic tests in two cases. One was for hemochromatosis, and one was for BrCA1, and the others, as Greg sort of reviewed with you, that was -- they looked primarily at that as just another clinical consideration about risk characteristics.

But I would commend to you these two reviews because it shows how the clinical guide or the U.S. Preventive Services Task Force applied their methodologies specifically to some types of genetic tests. And I'd be happy to talk about them more if you'd like.

As I said, we carefully consider the benefits and the harms and pay particular attention to

harms for screening tests. We are very much interested in the evidence of improvement in clinically important outcomes. Information alone that isn't related to outcomes is not going to be very persuasive to us. And the harms that we're talking about include not only the ones you might think of as directly related to false positives and so forth. But it includes labeling, anxiety, additional testing, false reassurances from false negatives. So we look at all of those and take them into consideration.

We also look at a variety of other considerations as we do these evaluations. We look at ways in which the use of the testing can be optimized, particularly through appropriate testing where, of course, family history can be potentially important and by identifying particular risk groups that might -- that are asymptomatic that might warrant screening.

We often, although we've been less explicit about this, consider the incremental benefit compared

to existing standards of care and existing technologies. As we try to translate the evidence

into recommendation, we also consider contextual factors including the time and economics and opportunity costs, if you will, as well as the nature of the condition, the severity, the availability of alternative therapies and so forth.

Very much like the U.S. Preventive Services Task Force, we think the bar is likely to be much higher. And we think it is higher and consider it higher than for other applications. We basically, as the U.S. Preventive Services Task Force, really try to make a recommendation based on two considerations: How certain are we that we know the answer to the question. We need to be at least moderately certain that we have the information correct, and that we can assess what it is. And the second is then, the magnitude of affect, and it needs to be at least moderate or greater. And I understand these are subjective terms. So we need to be able to make a recommendation in favor of the use of a test. We need

to be moderately certain that there's a moderate or greater benefit of this test.

There's a lot of methodologic challenge in doing all of this work. One of them is, how do you titrate the evidence to the problem. This becomes a particular issue since the technologies are changing all the time, and it makes it -- oftentimes, the studies that we use for assessing them relate to technologies as they were not as they are.

We're looking at how one can use modeling to be able to do some of these assessments, and we've done some of that on various occasions. We don't formally conduct economic evaluations, but we certainly use them when they're out there. And we talked about using more adaptive or staged processes so we can get much more efficient. Because as many of you know, the systematic review processes can be very long, tedious, cumbersome. So we've looked at ways that they can be streamlined. We pilot-tested some of those methods.

And again, I'd commend to you the review on

hemochromatosis from the U.S. Preventive Services Task

Force, which showed how you can obviate the look for a

lot of information when you can get the answer to one of the links in the chain that tells you that you can't complete the links and don't have to necessarily look at all of them.

So to sum, we think that for preventive applications of genomic tests, the bar should be high. The same is for other clinical preventive services because at that time, you'll know when you've got a valid, useful test, although we don't consider reimbursement as one of our primary audiences. Our work is primarily for clinicians. It will allow the - - we believe that it will reenforce the need for good reimbursement and that it will diminish the potential for harms, which is a major concern of ours, and that we have strong evidence for moving forward.

So with that, I'll stop.

Thank you.

DR. SATYA-MURTI: Thank you very much, Dr. Teutsch. It's very interesting that when we were in

the trenches as Medicare medical directors, we would often be asked and told that science follows practice,

and so one of your slides reminded me of that. We have some time, perhaps another 15 minutes or so for questions. I just have one question, and then we'll follow with the others.

One, the clinical utility in the outcome, what would be some of the major or pivotal outcomes you would look for that those measures are applicable across all age groups including Medicare age group? It varies depending on the test and the disease, but still for all of them -- and so-called overarching outcome, survival or feeling better, and then is it culturally determined and economically determined?

DR. TEUTSCH: Less economically determined. There is -- we have published, if you will, the outcome table as to what we think are useful outcomes that we will assess in the report on the oversight of genetics that was done by the secretary's advisory committee on genetics, health and society. And it's a long list, so I'm not going to be able to recite them

for you. Hopefully, in a forthcoming publication, you'll see them laid out more carefully.

But, in general, we look at a variety of them. And again, we're not looking specific at preventive tests. We're looking at all of them. Clearly the most important ones are related directly to morbidity and mortality, quality of life. Patient preferences are definitely a part of that because they embody a quality of life measures.

We do look at societal impact as well as some of the potential consequences on family. So they're broad. What we try to do is then to translate it down into specific outcomes that are germane to the tests that we are talking about.

So for ovarian cancer, for example, the outcomes that were germane for a screening test clearly relate to the survival and life expectancy of women who would be screened. We generally do not look as an outcome, for instance, about reduction in tumor mass or anything like that because we do care about survival.

The downside of that, and it actually was pretty apparent, was that most of the women who are

screened and found positive are going to need invasive tests. So we were to verify their diagnosis -- so we looked very much at the potential harms that are then associated with a variety of diagnostic tests that are done to establish the diagnosis.

You saw that for SIP450. You could see what the outcomes were, that is, do you get people's depression under control faster, are their symptoms less, and do we really have outcomes for that? So we do tailor these -- the general outcomes then down to the specific clinical scenario that we're looking at.

And I would point out that we look at specific clinical scenarios. We're not looking at specific tests. This is not a technology assessment program in general.

DR. HAYES: I notice on slide 14, you emphasize that information alone unlikely to be persuasive. Have you been criticized for being paternalistic in this regard, that having information

patients might do something with it, that you don't get to start with? I have, for example, so that's why

I'm asking you.

DR. TEUTSCH: We get criticism all the time on lots of dimensions. I think -- and these were very lengthy discussions 'cause clearly people had different perceptions of what this is about.

A lot of these tests -- and again we're not looking primarily at geriatric age group. But a lot of these tests clearly can be informative to help people make a variety of decisions in their personal lives. There's no doubt about it. Clearly the whole issue of genetic counseling is based on helping people understand and use information.

Where -- so yes, we clearly understand that those are important issues. But where we came down is, we are talking about clinical applications of tests and are interested in the clinical outcomes. Does it make a health difference? That's not to say those other issues aren't valid, but that's the framework that we've used much as the U.S. Preventive

Services Task Force.

You can see the same controversies that

exist there. Yes. I'd like to know my X or my risk for Y. But if there's no specific action that flows from that that makes a health difference, we would not consider that sufficient evidence to make a recommendation.

DR. SATYA-MURTI: Very quickly, what was your example? Maybe I'm a little confused. You said you had --

DR. HAYES: Well, again I'm a medical oncologist. Classically, when we try to develop guidelines for use of tumor markers, the criticism we get is, well, patients want to know if they're negative or positive even if that doesn't change your clinical approach. And we've made the point, for example, ASCO tumor marker guidelines panel, as you have, that one should be ready to pull the trigger and make a clinical change that you know improves outcomes based on the results and that one shouldn't just draw -- turn over a rock just because there might be

something under it.

DR. SCHEUNER: So I just wanted to ask a

question about the outcomes. And your slide says, "Requires evidence of improvement in clinical importance -- in clinically important outcomes." And my question is, for whom? Is it just for the patient sitting in front of you, or is also clinically important outcomes that might result for family members?

And if we truly take a societal perspective, then I'm wondering, you know, we should consider that as well. So, for example, if I have a patient who has breast cancer, we do BrCA testing, we find a deleterious mutation, now I have very important information for her relatives who are at risk.

And those relatives could benefit from that information and potentially reduce morbidity and mortality. And the guidelines that we practice in clinical genetics is to start testing in an affected family member first because that's where the bang for the buck is, so to speak.

20 And there are certain single-gene disorders

21 where doing that testing may not change the health

care I'm going to provide for that patient, but certainly would change the health care for those family members at risk.

DR. TEUTSCH: You're right. I think if you look at what the USPSTF did with BrCA that was certainly consistent. The EGAPP has just completed its review of Lynch syndrome, HNPCC, screening which deals exactly with this issue and basically came down with a recommendation that it was worth screening.

Now, that assumes that there are some relatives out there who could stand to benefit from all of this. Right?

DR. SCHEUNER: Sure.

DR. TEUTSCH: So it is contextual, you know. If you're the only surviving member in your family, and you're 70 years old, it's probably not worth doing a test. But there are others for whom it is, and we try to identify who they are. So the answer to that is yes, if we are not looking solely at the patient.

But we would then go back and say well, does it affect, let's say, the patient. In this case you

might say surveillance intervals should be different. Or in the case of a family member we'll say, if they are screened, and we talk about how one might do that, should their recommendations for screening for colorectal cancer be different than for the general population, and you'll see that. I believe that was published in January, the same issue as the methods paper.

DR. SCHEUNER: Right.

DR. TEUTSCH: So the answer is, yes.

DR. SCHEUNER: So I have another comment or would like you to react to another statement. So this clearly would be the case for the single-gene disorders again. But I'm not so sure it would be the case for the complex conditions where the alleles that are looked at, I guess, are generally more common. And perhaps, you know, if testing were made available, we had a great test that was predictive of cardiovascular risk, and there were interventions

20 available targeted to that and so forth, that I'm not

21 -- I don't know myself if family-based type of testing

would be indicated, so to speak.

So perhaps again it's apples and oranges. I'm trying to -- for the group as we consider again, how we're going to answer these questions, should we be dichotomizing things or not.

DR. TEUTSCH: I think we wouldn't necessarily frame the question that way. And I think if you could see that even under the SIP450, we will say, what is the test, what is the information provided, does it make a clinically important difference?

So if you're going to assess cardiovascular risk using a panel, say, of genetics, the question is, does it provide some incremental benefit in terms of cardiovascular outcomes in terms of, is it going to change the management, is there evidence that it changes behaviors in a way that we think is -- you know, we can be convinced -- actually makes a clinically important outcome.

DR. SCHEUNER: Right. But I guess what I was trying to say is, I don't think it has the same

level of importance for family members as does the rare single-gene. I'm not sure myself, but I would say --

DR. TEUTSCH: That's probably true.

MS. RICHNER: Just being a layman and being practical again, you're weighing heavily this last issue, which is the clinical outcome if there's some way that you're going to essentially change that. And you're deciding that based on the available clinical literature that has randomized studies and this kind of thing, to prove that there's a clinically-meaningful outcome of this screened condition.

My worry is -- and I'm always a pragmatist in thinking about timing. So, for instance, if we decide now that we're not going to approve that these screening tests have -- are related to a positive clinical outcome, you have to do all of the studies, the clinical -- it's 2010 now. That means, given what it takes to do all of the randomized control trials

and these kinds of things, we're not going to screen.

We're going to wait ten years to get all of our

randomized control trials all completed, and then have a clinically meaningful result in order to screen. I'm just having a hard time with all of this.

DR. TEUTSCH: And this is a great source of angst because ten years from now, the technologies are going to be different. And are we fighting the last war, too? So we share all of that. We're looking for methods that could be more efficient. Then the question is, how do you get to a sufficient level of certainty?

The case we would make is that in the prevention world, there are many harms that can be a consequence of tests. There are false positives, there are all kinds of -- it leads to diagnostic cascades. And, in fact, the risks of having -- of those are quite high so that we think that it is imperative that it is better for us to wait until our level of certainty is high enough so that we can be -- so that we can actually recommend them.

20 And you'll note the Preventive Services Task

21 Force, for instance, over time has been very

criticized as extremely conservative. Sometimes that's proven very good, and sometimes it hasn't.

MS. RICHNER: So you'll have to triage the top illnesses for the 65 and older that are the most costly to our society, that have the best opportunities now for treatment now. That's what you're saying.

DR. TEUTSCH: Yes.

MS. RICHNER: Okay. So we have to pick those top.

DR. TEUTSCH: Right. I mean, screening should be done for things that are important, reasonably common, and that you have something you can do something about. So, yes. Those are basic kinds of things. And particularly for the elderly population that's -- there are lots of them. And as we've talked about it, many are about qualify of life and other kinds of measures.

MS. DAVENPORT-ENNIS: Dr. Teutsch, I'm Nancy

Davenport-Ennis. I'd like to thank you for an outstanding presentation. I'd also like to thank you

for the article that you referred to in your slides. I would also like to draw attention to the same slide that two of my former panelists have addressed. And point number three, I think, is particularly important to the patient population as we look at examining the balance of harms and benefits.

I'd like to call your attention, if I may, to the paper that was provided to the panel for review. That calls out on the second page in the review of evidence section. And in this section you're talking about the fact that one of the procedures available for reviewing evidence is through metanalysis. And if I may, I would like to quote from the paper.

"Evidence reviewed strategies. When topics are selected for review by the EWG, CDCs, NOPHG commission systematic reviews of the available evidence. These reviews may include metanalysis and economic evaluations." Within this same section of

the paper, the immediate following paragraph.

"This statement is made. However,

comprehensive reviews are time and resource intensive, and the numbers of relevant tests are rapidly increasing. Some tests have multiple applications and require review of more than clinical -- one clinical scenario."

My question to you is, how much of this focus in the review process do you think will, indeed, revolve around the cost? And as we look at those opportunities and those costs, if we, indeed, know it's going to take multiple tests to come to some of the determinations that we need to, ultimately what will be the individual value to the patient through this process and to the societal good through the process?

DR. TEUTSCH: I think I heard a whole bunch of questions in there.

MS. DAVENPORT-ENNIS: There are two fundamentally.

DR. TEUTSCH: One was about the economics.

MS. DAVENPORT-ENNIS: That is correct.

DR. TEUTSCH: And the other was about the value to the patient.

MS. DAVENPORT-ENNIS: And societal good.

DR. TEUTSCH: And societal good.

MS. DAVENPORT-ENNIS: Right.

DR. TEUTSCH: And as I said, I think -- let me take the societal good and the value to the patient.

We're really talking about the trade-offs again for harms and benefits. If we were very convinced that harms were negligible, then the level of certainty that one actually needs on benefits is actually not that high a hurdle.

I'll give you an example. If you ask -- a clinician advises you to exercise more, okay? And you ask me, what's the evidence for that? Well, we gave it a pretty neutral kind of recommendation on the U.S. Preventive Services Task Force 'cause there isn't a whole lot of evidence. Right?

20 On the other hand, we would say we're

21 uncertain, but are encouraging, because the harms are

likely to be small, the benefits are likely to be -- are potentially substantial, even though we have uncertain -- we would probably, if you will, give it a positive spin.

So we do look at these things and try to get that assessment so that we can have reasonable level of confidence that what we're doing is more benefit than harm. So that's the way we would look at it and that would be true of an individual as well as with a family.

Now, in the individual clinician looking at an individual patient as opposed to this general societal population, let's kind of consider that individual patient. I mean, personalized health care is not new to clinicians. That's the business that they've been in for generations.

So they look at those particular things and specific harms and benefits that are likely to accrue to that patient and that patient's preferences. So

that's part of the consideration.

In terms of economics -- and I guess we'll

get into all of this later -- the EGAPP has done relatively little because there's been relatively a paucity of information for what we've looked at.

We are saying that it is a relevant consideration. Certainly opportunity costs in terms of time and energy and effort, both on the part of the patient and the physician, are important. Even the U.S. Preventive Services Task Force has now moved to that perspective, and then do not look at costs.

Having spent a lot of my life getting involved in economic evaluations, and -- well, let me turn -- let me tell you what we have done with the -- on another group, the National Commission on Prevention Priorities.

We have prioritized the things that are actually recommended that are effective based on their preventable burden, that is, how much societal good would there would be and their cost-effectiveness using a standard set of methodologies. Basically

those are the panel on cost-effectiveness and health and medicine.

Here's the take away. The take away is, that there are man orders of magnitude difference between the things that are most effective and the things that are least effective, even though they are effective. And there are orders of magnitude difference in their cost-effectiveness, too.

And we could quibble about small differences, but we are talking about enormous differences. So that one can get a fairly good handle on that. So well, you could say yes, it would be nice if we had time and energy to do all of these things. You can look at the things that are the most important to do and begin to set some priorities.

Now, that's primarily for clinicians, not for payers. But I can tell you, for instance, giving -- recommending people to take aspirin -- adults to take aspirin compared to making sure you get a tetanus shot every ten years once you've had an initial booster or your initial series, it's an enormous

amount of difference. And if we spend our time doing

the things that have the smallest preventable burden

and are least cost-effective, we are frequently missing out on those other opportunities.

So we think it can be done and should be done. Whether that's part of the original evidence process or not, that remains to be seen how we incorporate it. We just haven't had the opportunity very often.

DR. SATYA-MURTI: One more question, maybe.

DR. SPERTUS: First of all, I want to applaud you on the very scholarly logic that you've applied to try to evaluate the evidence. One area where you've remained silent on that I think is very important and germane to this discussion is around the end part of your spectrum of translational research, moving it actually to practice.

And my concern is, if you take the example of carotid endarterectomy, there are big clinical trials that show a benefit in symptomatic patients. But to get intersection at clinical trial, you had to

have a pari-procedural complication rate of less than three percent. And if you got much over that, the

risks out-weighed the benefits.

We have a flurry of physicians out there, who don't really remember genetics and learned it long ago. We don't have the infrastructure for genetic counseling that's throughout the system. And more importantly, I fear that we're going to run into a time where, you know, you're looking at a patient who has a very small risk of cardiovascular disease by their genetics or no risks from cardiovascular disease, but they smoke, and they eat terribly, and they don't exercise.

And we aren't creating the infrastructure for multi-variable models to integrate genetics as one factor of multiple factors that are going to create a much better spectrum of risk for the patient.

And I was wondering if you could comment on some of those challenges. Because if you approve a test, and in Atchison, Kansas, where, you know, I live, they just check a box, and they get this, you

know, bracket one possible. And I don't know what

that means. And how do they communicate that to the

patient, how do they figure out what to do about it?

I mean, there are a lot of challenges in the actual deployment of these complex tests that I haven't been able to read much about. The AHA has alluded to it tangentially. What would be your recommendations, and is EGAPP going to start to think as scholarly as it has about the evaluation of the evidence on the translation of that evidence into practice?

DR. TEUTSCH: You want a 25 word or less answer, I think. But that's a complicated and important question. And when it's -- we actually do look about -- at how well it can be actually implemented in practice. And to use -- I'll go back to the U.S. Preventive Services Task Force and what you talked about in terms of endarterectomy. That's exactly where we came down.

That, in fact, entirely selected centers, it might have some incremental benefit. But in general

practice, the harms are

-- you know, the mortality is higher than that and,

therefore, you know, should not be -- not generally be used.

So we do -- we tend to look at those things when we have that kind of information. But as I was alluding to for the National Commission on Prevention Priorities, these things should not be looked at as equal. And that we do need to have processes, whereby we look at their relative comparative value in a more holistic sense.

We're not doing a great job of that at the moment because most of our tasks are very focused. The attached -- EGAPP is an umbrella group, and the working group is the group that's been developing the methods and the recommendations.

There is also the EGAPP stakeholders group, which is -- has a much broader constituency. It's much -- and it has much broader representation from different groups, whether they're consumer groups, professional groups, payers, employers, you can -- and

a bunch of other, which I can't recall off the top of my head. But it's a big group of stakeholders.

And part of their job is to, A, identify technologies that are relevant to them and important, that they want assessed. But also to figure out how do we get these things out in a proper and efficient manner? So although that wasn't what I was asked to speak about today, and I'm not part of that stakeholders group, within the broad EGAPP framework, that's part of it.

And, as you know, with U.S. Preventive Services Task Force, on a smaller scale they have a program about putting prevention into practice. I talked to you about NCPP, which is a prioritization process. So these are baby steps along the way, but you know, I think this is a problem in health care. I'm now going to put on my public health hat. You didn't ask me for that, but you know, if you look at the real determiners of health in this country, it's not specific genetic tests.

The big determiners are social, economic,

and the physical environment. And if we really wanted to start putting our money where our mouth was, we

would really be investing much more in the -- in making societal decisions that will talk about dealing with really underlying determinants and those kinds of things.

DR. SPERTUS: Right. So to be more specific, I mean, would you recommend delaying the sort of widespread approval and dissemination of screening tests for genetics until we build that infrastructure to be able to translate into practice and understand how to translate into practice, or do you think that that's too high a bar, and that's moving things -- the fulcrum too far to the right?

DR. TEUTSCH: Oh, ideally in my academic sense, I think that's what we should have. I think the problem is that we're in a realistic world. We're in a free market economy where these tests are out there and can be used. And part of our job here is to get an assessment of them now so that we can inform these decisions. Ideally, yes. That would be nice to

do that.

But I think realistically we try to strike a

balance between staying abreast of these technologies, assessing them, getting them out there at the appropriate time, and making sure that people understand what the value is, so they can make good choices.

As Greg told you, you can spend all your -- all week, every week, to doing preventive services and not doing the rest of clinical care. That wouldn't be a very smart choice either. And we've got to help clinicians make good strategic choices about how to spend their time, money and time of patients, and energy and commitment.

DR. SATYA-MURTI: We have 30 seconds for the last question and 30 for answer.

DR. SCHEUNER: You pointed out in your slide that today, we were focusing on disease screening and, with respect to clinical validity, the association with the disorder. But actually, the row below, I think, is what we've been discussing. And that is

risk assessment and susceptibility and the association with the future disorder.

I mean, most of genetic testing that we've been talking about, DNA-based testing of heritable traits whether they're single-gene disorders or complex disorders, really relates to risk stratification and the added value I would hope to an overall risk assessment -- and was pointed out, and its ability to improve dissemination in its ability to reclassify individuals for whom then there would be an intervention available.

So we touched on this actually in February, when we were discussing diagnostics. But it's more relevant today in talking about risk stratification and all of that. And where do those intermediate outcome variables like improved reclassification, improved discrimination -- where does that fit in the EGAPP box?

DR. TEUTSCH: Well, it's interesting you ask that because, you know, that is, perhaps, a type of screening. When people talk to me about screening, I

think about early detection.

DR. SCHEUNER: I agree. But that's the way

it's defined for this panel today as both early detection and prevention, which relates back to risk assessment. If we could be instructed that we're only dealing with early detection, then that's a very much different scope for us today. So if we could know what we're supposed to be addressing, it would be extremely helpful.

DR. TEUTSCH: Let me make a comment on that. We would hold basically to the same evidentiary standard about clinical outcomes for risk assessment. That is, if you can assess, sort of -- first is the validity question. Does it assess the risk properly?

But the second question is still the same. It doesn't differ much. And that is, what is the clinical utility of that assessment? Does it then lead to some intervention, some behavior, or a decision process that is actually going to enhance clinical outcomes? I would say the same.

DR. SATYA-MURTI: That's good. At this

point I think -- Maria says we're allowed to use the

bathroom. So I think we should -- that's on the safe

zone. It's not in the red zone. We ought to be doing that. I'm sorry about truncating this, but we have time for among-panel discussion mid-afternoon. So if we may break and come back in exactly 15 minutes? Thank you.

(Whereupon, a short recess was taken.)

MS. ELLIS: We will now start the public comment section. First up we have Dr. Jan Nowak.

DR. NOWAK: Good morning. My name is Jan Nowak, and I am a pathologist and Medical Director of the Molecular Diagnostics Laboratory at Evanston Hospital in Evanston, Illinois. And I invite you on behalf (unintelligible) talking about something other than the swine flu.

I'm here today on behalf of the College of American Pathologists, where I'm a member of the Patient Safety and Performance Measures Committee and the Molecular Oncology Committee. The college appreciates the opportunity to appear before you today

and provide our perspectives on evidence requirements for using genetic tests for disease screening.

The College of American Pathologists is a national medical specialty society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. Our members have extensive expertise providing and directing laboratory serves and volunteer as peer inspectors in laboratory accreditation programs. The college's Commission on Laboratory Accreditation is responsible for accrediting more than 7,000 laboratories here and abroad.

I have two points that I want to leave you with today, and I think these will reiterate some of the comments that our speakers made earlier and hopefully will help you in your task.

Firstly, college members feel that genetic screening tests are not unlike numerous other laboratory tests that are used for screening purposes in medical practice and should be evaluated in a

similar manner.

In the college's comments to this committee

in February, we highlighted the role of pathologists in developing, delivering, and interpreting genetic and genomic tests for patients.

In the treatment of an individual patient, a pathologist interprets the date produced in the laboratory in the context of the patient's clinical situation, including family history, and participates in interdisciplinary discussions involving primary care clinicians and other specialists regarding which tests to order, the significance of test results, unusual or unexpected results, and recommendations for additional testing. We think this process ensures the best test selection for each specific patient.

The goal of screening programs, however, is not simply to ensure the right test for the right patient at the right time, but to ensure that at-risk individuals in a population be identified early enough to prevent disease progression or provide interventions that improve patients' outcomes.

The focus of screening tests is not so much

on the choice of tests but rather that the patient

come from a select already identified at-risk population. The screening test has as its overriding purpose not simply diagnosis but identification of individuals with increased potential to develop disease or to develop more serious disease.

So acknowledging that shift in focus, it is no less important that screening tests be evaluated in the context of well established performance characteristics common to diagnostic testing. As noted in the materials that was distributed to the committee beforehand, the important criteria for a screening test includes simplicity, acceptability, accuracy, cost, precision, sensitivity, and specificity. These criteria are common to all clinical tests.

What distinguishes screening tests here is the importance of identifying the correct population in which they should be used.

Now, it's convenient for us to equate

asymptomatic with absence of disease but this morning

I've heard various definition of what asymptomatic is.

I've heard it's absence of disease. It's asymptomatic, absence of symptoms. I've heard one speaker talk about absence of signs and symptoms. I've heard another speaker talk about pre-symptomatic disease or pre-symptomatic lesions. I mean which is it? I think we need to acknowledge what it is we're talking about. So to say that our population is asymptomatic and without disease, that's not entirely accurate. Every individual in an at-risk population has some probability of harboring disease. There's no question that all of us in this room are at some risk for the development of colon cancer but we don't screen 20-year-olds for colon cancer. We are selective in who we screen. Likewise, there's -- the women in this room all have some risk for cervical cancer or for breast cancer, but we have clinical guidelines to tell us where we apply those screening tests that we have.

The function of the screening test is to

revise the risk of disease either upwards or downwards and then proceed accordingly. The goal of the

screening test is to inform us how to best utilize our resources to prevent disease progression or to prevent disease development.

Secondly, it's critical in your deliberations that you distinguish the various forms of genetic tests. Genetic screening tests for common Mendelian disease, cystic fibrosis, for example, these have been well established using conventional evidentiary processes and mechanisms. Similarly, genetic tests that identify inherited variations in physiology and metabolism, that path of physiology that Dr. Teutsch talked about, say for example Factor V Leiden testing as the basis for inherited resistance to activated Protein C or even CYP 2C9 testing for warfarin. I mean all of these have well documented biological underpinnings.

We understand the pathophysiology. These are not simply associations. We understand the biology of these diseases and the evidence behind them

is in the scientific and in the medical literature.

Likewise, genetic tests for acquired somatic

mutations, the kind that are etiologic for cancer, are not a difficult issue. A screening test to identify some of the mutations currently found in colon cancer, for example, is not founded simply on statistical association, but rather is rooted in the biology of tumor development.

These kinds of genetic tests where the genotype/phenotype relationship is understood sufficiently to define the disease process, these need to be distinguished from genomic association studies where the function of the genetic variations are unknown, where the genotype/phenotype relationship is purely or largely associative.

Those tests spawned by Genome Wide Associations Studies are unique. And they raise unique concerns that I'm sure this panel will hear about later today. And we think for those, outcomes will be particularly important and carry a particular weight.

So in summary, as medical specialists in the diagnosis of disease, pathologists have a long track

record of practicing evidence-based medicine through the development of appropriate laboratory tests and the selection of alternative diagnostic methods.

Screening tests in general are not different from other diagnostic tests in their validation. But the use of a particular test needs to be considered in the context of the goals of the screening program.

The CAP also encourages the panel to recognize the need to distinguish the different types of genetic tests as it considers the kinds of evidence needed to establish a particular test for screening purposes.

We're very willing and happy to contribute our expertise in these discussions. And I thank you for your attention and the opportunity to share these remarks with you.

DR. WENSTRUP: Good morning. My name is Richard Wenstrup, and I'm the Chief Medical Officer at Myriad Genetic Laboratories, Incorporated, located in

Salt Lake City.

Of course I have a financial interest in

Myriad, but no other conflicts of interest. I'm a physician boarded in Pediatrics and Clinical Molecular Genetics. I can provide my CV if the panel so wishes.

I want to thank you for the opportunity to provide you with information regarding diagnostic testing for hereditary cancer syndromes in the Medicare population.

Local Coverage Determination for Genetic Testing outlines clinical criteria for medical necessity for three hereditary cancer syndromes, including Hereditary Breast and Ovarian syndrome, the Lynch syndrome, and the Adenomatous Polyposis syndromes.

At this time, only Medicare beneficiaries who have previously been affected with cancer and have a significant family history are covered. The coverage determination specifically states that unaffected patients are excluded from coverage even when a mutation has been identified in the family,

where they'd have up to a 50 percent risk, to, quote,

"Testing of unaffected family members or other

individuals is considered by Medicare to be screening and is not payable under the Medicare program."

Myriad takes issue with this -- with this last notion that testing of unaffected, at-risk individuals is necessarily considered screening. And I hope to elaborate in the next few minutes.

Genetic testing to identify patients who have a hereditary risk of cancer has become standard of care, and numerous professional societies have published position statements on the appropriate use of these tests.

These guidelines reflect the fact that genetic testing of unaffected individuals with high-risk family histories is medically appropriate with substantial clinical utility.

As opposed to general population tests, such as Pap smears and mammograms which are offered to all patients regardless of signs or symptoms, a specific genetic test for hereditary cancer risk is only

recommended for unaffected individuals if there is a

family history of cancer that meets really -- meets

specific high risk criteria such as early age of onset, multiple affected family members, et cetera.

In essence then, the affected individual's family history of cancer is the sign or symptom that prompts genetic testing. Family history is a key part of medical evaluation and has always guided the decision for medical testing. A positive test in an individual is diagnostic and leads to a specific set of recommendations for increased surveillance and occasionally preventative surgeries.

A clinical consensus has emerged around the use of these tests. And we think that Medicare's coverage for its beneficiaries falls short -- falls short of that clinical consensus.

The USPSTF published a clinical guideline on Genetic Risk Assessment and BRCA in 2005. They recommended that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or 2 be referred for genetic

testing and evaluation for BRCA testing.

In addition, the NCCN or the National

Comprehensive Cancer Network's guidelines on hereditary breast and ovarian cancer suggest the evaluation for high-risk unaffected individuals as do those of the Society of Gynecologic Oncology and recently the American College of Ob/Gyn.

In Myriad's view, exclusion of these tests for appropriate patients may result in substandard medical care for the beneficiary. Mutation-positive individuals remain undetected and therefore unable to take the necessary steps for risk reductions.

To use hereditary breast and ovarian cancer as an example, the published medical management recommendations for a BRCA1 or BRCA2 carriers apply to both unaffected and affected individuals. They have a -- the positive BRCA1/BRCA2 mutation carriers have an up to 87 percent and 44 percent chance of developing breast or ovarian cancer respectively, in addition to a significantly increased risk of cancer of multiple primaries.

For BRCA1 mutation carriers who are of typical age for Medicare coverage, a significant risk

of cancer remains. In the 2007 meta-analysis, Chen reported that a 60-year-old BRCA carrier has a 17 to 19 percent chance of developing breast cancer and a 10 to 22 percent chance of developing ovarian cancer by age 70.

Proven intervention -- medical intervention such as prophylactic removal of breast or ovarian tissue can reduce the respective occurrence by over 90 percent.

Among patients with Lynch Syndrome, the risk of colon cancer and endometrial cancer also persists well -- well into -- well beyond the sixth decade. And Henry Hampel in 2005 calculated the mean age of onset for cancers in Lynch Syndrome was 58 years old.

Individuals with Lynch Syndrome should undergo colposcopy every one to two years due to the risk of cancer. And frequent colonoscopy has been shown to reduce morbidity and mortality from colorectal cancer in this population.

Finally, we analyzed our own data from the years 2000 to 2009 and found that five point six

percent of all patients found to have a deleterious mutation develop their cancer after the age of 65.

It's presumable that if they have been identified and tested before developing their cancer, they could have taken preventive measures to reduce the risk.

Rarely is family history of colon cancer alone sufficient to warrant the kinds of significant changes in surveillance and possible surgery that would clearly be recommended if the patient had a positive mutation.

There is significant medical and economic value in proactively identifying mutation carriers prior to the onset of disease. A recent publication by Holland, et al. determined that genetic testing of B1 and B2 genes for unaffected women is cost effective -- would be cost effective even if the criteria for current guidelines is reduced.

The downstream benefits of identifying

20 individuals with mutations and then doing the same

21 with their family members would lower the incidence of

cancer in those who would ultimately become members of the Medicare population. The resulting social benefit of health care savings and ultimate reduction in overall cancer incidence should not be overlooked.

In conclusion, we would like to thank the committee for the opportunity to comment on their current criteria available in supporting the test of unaffected Medicare beneficiaries. We believe that there is currently sufficient evidence to support hereditary cancer testing of beneficiaries with significant family history and strongly encourage a change in the coverage criteria.

Thank you.

DR. SATYA-MURTI: Dr. Quinn, you're next.

DR. QUINN: Hi. Bruce Quinn. I'm a full-time consultant with Foley Hoag, LLP. I don't have any -- I've worked on a lot of associations, health plans, manufacturers, as a consultant over several years. But nothing that's a specific product that I'm

representing or working on in genetic screening tests.

What I'd like to talk about for a few

minutes is to put a couple stakes in the ground for you on the theme that it's not always a clear line between a screening test and a diagnostic test and then tie those things together on the summary slides. So you will have the feeling I'm kind of planting a couple things out there before I tie them together.

The usual view is that screening tests are like way over on the left and diagnostic tests are way over on the right. Colonoscopy every ten years is a screening test. But if you have personal signs and symptoms, it's a diagnostic test. And Medicare policies and codes reflect that.

For example, there's a benefit for screening for prostate cancer. It's in the statute, and you can get either a digital rectal exam alone for $20 dollars. I don't know who specializes in doing that. Or you can get a PSA alone for $25 dollars. And that's a standard every year screening benefit.

Or you could have personal signs and

symptoms of prostate disease, in which case there's a different code that's a diagnostic prostate test. If

you get into the diagnostic prostate test, there is an NCD that has dozens and dozens of ICD-9 codes attached to it.

And they include things as broad as hypertrophy of the prostate. Well, everybody over 45 has hypertrophy of the prostate at least without symptoms. So that would virtually cover everyone. And then you'd have almost a complete overlap between BPH with no lower urinary tract symptoms and being over the age of 50. So those things certainly blur into one another.

But there are other examples where Medicare has made distinctions between a condition versus a disease. For example, smoking has an ICD-9 code. But if you take smoking, and you add a condition like emphysema to it, then you can get into the smoking cessation counseling benefit.

So smoking alone doesn't qualify for that. But smoking and emphysema, shortness of breath, heart

disease, would qualify. So they distinguish between

smoking and the smoking-related condition.

Now, I've always puzzled about this. If you've got hypertension, you can be diagnosed and treated for hypertension. If you've got coronary artery disease or stroke, we'll diagnose and treat that.

But you could argue, based on the previous slide, that nobody has ever died of hypertension. You only die of things caused by hypertension like stroke and heart disease. Just like you could say you don't have smoking as a disease, only things that it causes.

So we don't treat those things symmetrically. And either there's some difference that people see when they think about them. Although you could take an angle that those columns are pretty similar.

Now, if you've got diabetes, we'll do glucose testing, A1c testing, and treatment. If you've got signs and symptoms of diabetic retinal disease, you come in and say, "I've got diabetes. I

don't see as well the last two months," and you get a

diagnostic retinal exam.

What about an annual retinal exam? Up until -- through the last five years, I was a regional Medicare medical director. And I remember teleconferences where people talked about is that annual retinal exam part of managing diabetes, or is it a screening test for something the patient doesn't have which is diabetic eye disease.

And there were lively conversations about that, most people feeling that it was part of the medical management of something. A different disease, but a disease related to hyperglycemia and diabetes. So it wasn't a screening test.

Well, if you're diabetic, you can get nerve conduction problems as well. Do you get an annual nerve conduction exam? No. People thought that would be a screening test. And therefore, it's not a Medicare benefit.

If you have chemotherapy, you can get hematocrit testing because you might get anemia caused

by your chemotherapy testing. However, it's a risk.

You don't actually have any signs and symptoms of

anemia. You just have one thing, chemotherapy, that might be associated with a different thing, anemia, for which there's a diagnostic test.

If you try to rationalize what we're doing, there is a benefit not for a diabetic retinopathy exam, but for a glaucoma screening. And you get that in people who are diabetic or African-American or Hispanic or have a family history of glaucoma.

So there's a point where family history comes in. But that's a statutory benefit. It's not a general benefit.

Now, you might have argued if this didn't exist that people with diabetes would get a glaucoma exam as part of the management of their diabetes. Maybe it would be a reasonable and necessary part of managing diabetes. But here, it's unlike the other exam. It's being viewed as a screening benefit.

So in summary, I would say that how can you compare family history to this? Well, family history,

as we saw this morning, is an integral part of the H and P. I had no connection a month ago with Dr.

Phurrough when he wrote his slides.

Family history certainly affects testing in the presence of a minor symptom. You know, if you've got someone with an earache or someone with an earache and five family members with acoustic schwannomas, you're going to treat it differently based on family history.

Obviously, as soon as a sign or symptom occurs, then we would use family history, and nobody would question that.

There is nothing in the statute -- although I'm not an attorney, I've worked with Medicare for years. There's nothing in the statute that excludes family history. It's a custom.

And so I think where family history, I would offer, has a greater impact than signs and symptoms that already qualify for the same test, it should be reasonable and necessary justification.

So that the test itself be reasonable and

necessary to manage the patient would be the key

factor, and not the form of the medical history, like

whether it's family history or not.

So that would add family history to the rationale. But that would not include population screening tests per se. It would be for tests for increased risk.

There are times when we do things for the beneficiary that involves someone else. For example, if a patient's in a coma, the doctor gets paid for interviewing family members for family history or other management decisions. You can bill that.

If the patient's schizophrenic, you can go to the family for the medical history as well as the family history, social history, history of allergies, and so on. So there are some times -- this might be a bit of a stretch -- where you do go to people other than the patient and get paid for doing things for them, with them, that are not actually hands-on or diagnostic of the patient itself.

Thank you.

DR. SATYA-MURTI: Doctor Eng is next.

DR. ENG: I'm Charis Eng from the Cleveland

Clinic. I'm chairwoman and director of the Genomic Medicine Institute, which is about three-and-a-half years old. I'm also the director of the clinical arm of that institute, the Center for Personalized Genetic Health Care.

I think for these purposes I have to say that I am on the board of scientific counselors of NHGRI. And I am chair of the Clinical Science Committee of the Personalized Medicine Coalition.

I brought a PowerPoint for the audience, but was not allowed to load it. So I really apologize to you. We don't have enough hard copies. The panel has copies, please be assured.

Since I'm a practicing physician, we love case histories. Let me start by someone that we all know. July 12th or 13th last year, ex-White House press secretary Tony Snow dies at 53. And every press release says he died of colon cancer at age 53.

Well, that's sort of young. And it goes on

to say he was first diagnosed at the age of 49. They

did a surgery, underwent chemotherapy, and all of

that.

And the previous year, he had metastasis to the liver. He had surgery, which is unusual, and had chemotherapy. But he died.

And in only two of these news outlets it says in small print, by the way, his mother died when Snow was in high school. So her estimated age is 35 to 48. Again, family history could have informed.

So the most likely diagnosis is hereditary nonpolyposis colon cancer syndrome, HNPCC, or Lynch Syndrome, which you've already heard about.

Now, if he had only come to genetic counseling and genetic consultation at that time, we would have offered mismatch repair gene testing. Now, we always test with a known affected person. His mom was alive when she was first diagnosed. Whether we had HNPCC testing at that time is moot.

But you heard that it has 80 percent lifetime risk of colon cancer, and for women, 40

20 percent lifetime risk of endometrial and 10 percent

21 lifetime risk of ovarian cancer.

Tony Snow could have started screening colonoscopies at the age of 25. And by predicting his cancer risk, the family history leads to genetic testing and it predicts risk of precise cancers which could have been preemptively prevented.

So you're all saying, yeah, but he's not in the Medicare population. Last Thursday I saw a 66-year-old apparently healthy male who had a mom who wore a colostomy bag all her life and died of endometrial cancer at 50. He had five kids, one of whom died of colon cancer at 29.

We wanted to test him. We could not get blocks from either. Medicare does not cover this. And the patient was not pleased. His wife was enraged. I mean, many of us who practice, even though it's not us, if it doesn't cover, they're just enraged at us.

This is not a genetic -- it's not a screening test. This is in fact a diagnostic test of

an obligate carrier. And it absolutely will lead to

the change in management, not just of the patient, but

of the family members. So here it's family, society.

So we're all skirting around whether to use personalized medicine. And I prefer the use of personalized health care because it's very broad, all the way from clinical phenotyping, which is extremely important, to risk assessment and then to choosing management. Not just therapy, management.

Now, the concept of genetic based personalized health care is not new. Some say it started in ancient Egypt. You only (unintelligible) for certain things. But I think to be fair, ABO blood typing for safe transfusions is probably one of the earliest forms of genetic screening for treatment.

We are in 2009. I think you've heard that theme over and over again. So let's bring all of American health care into the real twenty-first century.

Now, when you say genetic screening tests -- and I think I harken to the first speaker -- it is

very broad. What do we mean? And I want to highlight

what we heard this morning just a little bit.

There are validated genetic tests usually for Mendelian traits. They can be used as a diagnostic. And I prefer the words, they can be used as a predictive test -- not a screening test -- of the as yet unaffected at-risk family members when there's a family-specific mutation identified.

It does guide clinical management. Let's separate out the variant-based statistically associated genomic testing. Right now, there's no clinical context for most. Some of them say all. Most of those genomic testing based on SNPs.

And we have to say that the standard goals of genetic testing, after all, like all clinical testing, is to make an accurate diagnosis, to reduce disease, and to identify at-risk people for prompt risk management. And the common symptoms go all the way from preconception, crib, to death.

I, for example, have chosen to be a clinical cancer geneticist. So the first take home message is

always gene test in the setting of a consultation

which includes genetic counseling. Yes, there's very

few of the genetic counselors. There's very few clinicians who practice. But we are thinking of novel ways so that we can build this infrastructure for a lot of genetic testing and interpretation.

So we always start testing with the living affected if there's one. And then predictive testing becomes 100 percent accurate.

So I would like to posit that state of the art genetic testing is analytically valid, clinically valid, clinically utile, and actionable.

So now to genomic testing. Price Waterhouse has identified some top health industry issues. And one of them is genomic testing has reached the price point so that the masses can buy it without health care givers' intervention, interpretation, counseling.

These, I would like to posit, have questionable analytic validity. They currently have little or no clinical validity, no clinical utility, and no actionability.

Since genetics contributes mightily 30

percent premature mortality, the time is now ripe for

us to bless using clinically worthy genetic testing in apparently unaffected individuals. And I would like to again emphasize the utility of the family history.

Now, clinically worthy genetic tests applies to virtually all Mendelian genetic diseases. The absolute indication is if you know the family-specific mutation, it's a hundred percent accurate, the test, in an apparently unaffected relative.

The other indication is, like my family, there's a linchpin member who might be an obligate carrier, or there are no living affecteds. And so the next living, quote, "unaffected" with the highest probability -- that's why you take the family history -- should be tested.

And so let me close by saying that family history is the first, the cheapest, and the easiest risk assessment to see if validated genetic testing should be used.

Thank you.

DR. SATYA-MURTI: Very good. Thank you.

That came out quite well, even without the PowerPoint.

Dr. Hawkins?

DR. ALLINGHAM-HAWKINS: Good morning. My name is Diane Allingham-Hawkins. I'm a molecular geneticist and a cytogeneticist. And I'm here representing Hayes, Incorporated, an independent health care and research and consulting company located in Lansdale, Pennsylvania.

For more than 20 years, Hayes has been an industry leader in providing health technology assessment on a wide variety of new, emerging, and controversial health technologies to our worldwide clients, which include hospitals, health care systems, managed care organizations, government agencies, and employers.

I am the director of the Genetic Test Evaluation Program at Hayes. Hayes does not, nor do I personally, have any financial involvement with manufacturers of any products being discussed. And my travel to this meeting was funded entirely by Hayes.

With respect to the evidence requirements for genetic screening tests, I would like to make the

following points. There must be clear definition of the disorder and the test being assessed.

Evidence requirements will be quite different for highly penetrant single-gene disorders than for genetic variants that predispose to disease rather than being truly predictive. To illustrate this difference, allow me to use the example of Huntington disease, an adult onset neurological disorder with virtually 100 percent penetrance for variants in the affected range.

If you have this allele, you will get the disease, assuming that you live long enough. Compare this to genetic variants in BRCA1 and BRCA2 genes which predispose to breast and ovarian cancer, but do not guarantee that the individual will develop the disorder.

Still less certain are single nucleotype polymorphisms or SNPs which provide very modest increases in predisposition. An example are SNPs on

chromosome 9p21 associated with coronary artery disease, an assessment of which I provided to the

committee as part of our submission and which I will comment on further when I discuss clinical utility.

The appropriate patient population must be clearly defined. Again, this will vary depending on the type of test and may depend on many factors, including sex, ethnicity, age, and family history, among others.

Important factors for analytical validity include analytical sensitivity and specificity, but also include appropriate pre-clinical validation of the assays, the inclusion and monitoring of appropriate controls, calibration of instrumentation, training and education of laboratory staff, including professional staff, and regular and successful participation in proficiency testing. Laboratory accreditation by all appropriate state and federal agencies is also a critical element.

Important evidence requirements for clinical validity include clinical sensitivity and clinical

20 specificity. The number of studies and number of

21 patients per study required to establish these

elements vary depending on the disorder and the relative predictive value -- predictive impact of the genetic variant.

A highly penetrant single-gene disorder requires fewer studies while SNPs with a small relative risk require a large number of studies with many well-characterized patients and controls in each study to validate the association.

Clinical utility is unquestionably the most difficult area to assess for genetic tests because few, if any, studies demonstrate the impact of the test on patient care.

Ideally, what you're looking for is a clear cause-effect relationship. Because you have this genetic information, patient care was improved. This rarely happens.

Even for highly penetrant single-gene disorders like HD, with the exception of reproductive decision-making, it is difficult to demonstrate the

direct benefit to the patient of knowing their genetic status.

There are certainly exceptions. And BRCA1-2 status in patients with significant family histories of breast or ovarian cancer is one of them, particularly when the familial variant has been identified.

Although carrier status for one of these variants does not translate to absolute risk, the risk is still significant, perhaps 65 percent lifetime risk for breast cancer. And there are preventive strategies that reduce risk.

However, for the majority of emerging genetic tests that might be applied to a greater proportion of the population, like the chromosome 9p21 SNPs, the evidence of clinical utility is just not available.

Despite a large body of evidence that demonstrates an increased risk on the order of 30 percent for myocardial infarction or coronary artery disease with these variants, there is simply not

enough evidence to suggest that knowing this

information improves patient management or clinical

outcomes.

There is no association with severity of disease. In addition of the genetic information to other common risk factors such as age, blood pressure, or cholesterol levels does not significantly modify risk.

There is a small amount of evidence that suggests that adding this information to patients with intermediate Framingham scores allows reassignment of a proportion of patients to low or high risk groups. But these data are limited to a handful of patients to date and require further validation.

Finally, I would like to address the ethical and social issues surrounding genetic screening tests. It is particularly important when dealing with tests that identify predisposition to, but are not diagnostic of genetic disorders, that issues surrounding discrimination and stigmatization are adequately addressed.

It would be very unfortunate, for example, if an individual tested using an association test for

MI or the APLE E-4 (phonetic) which is neither sufficient for development of Alzheimer's Disease would be considered sick in the absence of any other supporting medical information.

With that, I would conclude my comments. Thank you for the opportunity to address the committee.

DR. SATYA-MURTI: Dr. Klein is the last presenter.

DR. KLEIN: I'm Roger Klein. I'm representing the Association for Molecular Pathology.

So just from the perspective of a practicing laboratory physician, the approach and analysis of tests that we're calling genetic should not differ from those of other laboratory testing. The unique features and characteristics of screening programs far outweigh differences in test methods or modalities.

By definition, in the screening program, we're testing significant numbers of asymptomatic

20 individuals. Therefore, any harms that result from

21 that testing would not have occurred but for

implementation of the screening program.

Thus, there are potentially large public health impacts, both positive and negative, from screening programs.

And lastly, screening programs are expensive. Therefore, the standards of evidence by which the potential implementation of a screening program is initiated should be far more stringent for screening purposes than for diagnostic testing.

That being said, it's extremely difficult if not impossible to establish universal evidence standards for screening tests. Because of the heterogeneity of genetic testing, as others have pointed out, it's actually not possible probably to do that for genetic testing either.

And I think the analysis really depends upon the specific application. Are we looking at risk stratification, or are we looking for early detection? And while some have pointed out that the outcome

measures may not differ between these two, the harm side of the utility calculus may.

What is the specific disease at which we're looking and what are its features? How severe is it? What are the potential harms that could result from the specific screening program, and are there subpopulations with which we're particularly concerned?

All this suggests then a need for individualized analysis with flexibility being key. We don't have time to get into the details of genome-wide association studies. But let us just say that they do present unique statistical challenges.

Because of the multiple comparisons, often running into the hundreds of thousands in these studies, there's a high statistical likelihood of having false positive results.

There are other factors that potentially could bias results or could create false positive outcomes. And these do need to be addressed, and they need to be dealt with.

In terms of the evidence of analytical validity for molecular diagnostic tests -- and I'll

use that term, molecular diagnostic broadly -- most molecular methods that are used clinically are robust and offer excellent analytic performance.

The measures at which we look are analytic sensitivity, specificity, reproducability, linearity, and consistency in response to changes in analytic and pre-analytic variables. Some of -- or many of these tests have actually supplanted methodologic gold standards which does present a problem with respect to comparisons.

That being said, most of these tests are performed using a common set of techniques. There's usually broad experience with them. And there's frequently published data on methods available in various contexts, if not the specific context under study. For novel methods, of course, we need greater scrutiny and probably a de novo analyses.

So getting to the components of a screening program, we start them with a disease that has to have

a significant public health impact. We have to understand its natural history, and there has to be

interventions, not only available, but also accessible to the tested or screened population.

Tests need to have high analytic and clinical sensitivity and specificity. But these don't go far enough. And really, we need to look at the predictive value in order to assess the potential efficacy of a marker. And that predictive value depends a great deal on the prevalence of the disease or outcome in the patient to be analyzed.

In addition, there are other biases we need to address in these programs. This slide just gives a brief demonstration of the effect of disease prevalence on positive predictive value. If you have a 50 percent prevalence, the positive predictive value is almost a hundred percent for a test with 99 percent sensitivity and 99 percent specificity. Clearly a superior assay.

But you can see how quickly, even for such an excellent test, that the positive predictive value

drops off with each log reduction in disease prevalence.

So in conclusion, what I'd like to say that again, there's no -- there should be really no difference, no foundation difference in the analysis of genetic and non-genetic tests per se. However, the standards for screening need to be significantly higher than for diagnostics.

But that being said, that is said with the caveat that this must be done on an individualized case-by-case basis because of the differences in such tests.

And then finally, the clinical sensitivity and specificity, but more importantly, the positive and negative predictive values are extremely helpful in establishing the potential utility of a test as a screening marker.

Thank you.

DR. SATYA-MURTI: We might have some -- we have Barry Thompson. You have a couple of minutes for presentation.

DR. THOMPSON: I'm Barry Thompson, the medical director for the American College of Medical

Genetics representing the College today. And I have affirmed that I have no financial conflict of interest at this point. I appreciate the opportunity.

The College represents some 1500 M.D. and Ph.D. geneticists and other health care professionals. Most of our members are certified by the American Board of Medical Genetics which is one of the boards recognized by the American Board of Medical Specialties.

ACMG is particularly supportive of the incorporation of genetic testing and genomic testing into the practice of medicine in support of the 2008 report of the HHS secretary in his report on personalized medicine and in consonance with the direction and interest of the current administration and the new President.

I'd like to stress that a systematic approach to meeting the requirements for the evidentiary framework sufficient to implement testing

that's both medically necessary and financially

responsible and for the subsequent coverage and

reimbursement decisions that have to be made rests on several points.

And this was provided to the 25 February panel as a statement from ACMG, that the acquisition of data from clinical centers and settings sufficient in amount and representation of a target population to permit valid statistical analysis. It's also dependent upon the aggregation and storage of these data within a centralized virtual or physical information technology system for appropriate analysis, timely reporting, and for future access.

And lastly, the demonstration of the validity and utility of testing needs to be made prior to clinical deployment.

We seek to speak as one of the voices for the medical genetics community. We're an active participant in all aspects of the incorporation of genetics and genomics into medicine.

Several of our members speaking today and

here in the panel have special expertise in the

development and implementation of genetic testing for

the improvement of health. And we continue to be an active partner in the development and implementation of relevant policies.

So I urge the committee to continue to drum up the expertise that the American College of Medical Genetics, amongst our other professional colleagues in the specific area of genetic and genomic medicine.

Thank you.

DR. SATYA-MURTI: Okay. Thank you, Dr. Thompson. We're sticking to our schedule quite well, the importance of which is even more apparent in the afternoon, so we can catch our return flights home.

We have about 15 minutes. If there are questions for -- only for this presentation from the invited and Dr. Thompson today. Yes? Go ahead.

DR. HOLTZMAN: It seems to me, particularly in the first three presentations, that there is a lot of confusion about what is screening.

And I go back to the deliberations of really

the first federally convened panel, convened by the National Academy of Sciences in the early 1970s.

There's a publication still available called "Genetic Screening," in which the definition of genetic screening began with a search in a population.

Now, it seems to me that this is a distinction that's very important in terms of our deliberations today because a number of speakers have included in their definition of screening individuals who have been identified through a family history but who are asymptomatic where the availability or the use of a test is defined as screening.

Now, I don't think that in epidemiological terms that that kind of testing is screening. And it would save a lot of confusion if we could redefine as it was originally defined -- and it was also in the Wilson Youngner criteria for screening -- that it is a search in a population.

So that, for instance, Myriad's contention that coverage for testing for individuals who have a family history and documented BRCA1 cancer causing

mutations or cancer-related mutations should not fall

under the rubric of screening and should be allowed

coverage.

And I think a very simple solution for this panel is to redefine screening as it was originally meant to be, a search in a population and not in a high risk situation where there's a family history.

DR. SATYA-MURTI: Dr. Salive, correct me. Screening definition is statutory rather than left to the discretion of panel or within agency. Isn't that correct as it stands now?

DR. SALIVE: Well, I think we tried to frame it as -- under preventive services. So I guess I would really agree with Dr. Holtzman on this one, that, you know, if we want to discuss how can we cover genetic tests, it has -- you know, other than diagnostic purposes which was discussed at the last meeting, we're going to have to discuss it here as a preventive service.

And so, you know, can we change things in the future and recognize things differently? You

20 know, sure. I mean, Congress just gave us this

21 authority last year. And they may change it in the

future.

But currently, the only way we can cover this type of testing is as a preventive service. And so as was outlined by Dr. Roche, we have these three criteria. And so Preventive Services Task Force comes into play, reasonable and necessary comes into play, and appropriate for the Medicare population.

DR. SATYA-MURTI: Will the deliberations of this panel be of any influence on changing it, say legislatively?

DR. SALIVE: Well, that's impossible to say by me. So finally, another point I guess that's relevant. You know, CMS doesn't decide what's a disease. You know, we have to implement that in our coverage policies. But we tend to defer to others on that.

And so, for example, you know, people have talked about what's high risk versus what's a disease. We don't -- you know, we're not going to be in the

business of deciding that. We look to others for that.

And so, for example, we've discussed treatment of obesity in Medicare. And if -- at this time, we don't believe that the authorities -- we look to recognize that as a disease. And so we've artfully figured out how to cover certain treatments of the comorbid conditions associated with obesity.

And I'll grant you, that's something that those of us who, you know, work in Washington or live in Washington can do more artfully than others. I think that's where we are.

So we will look to people like the NIH, the Centers for Disease Control, for defining what's a disease and a treatment for a disease that we can look to.

DR. SPERTUS: I guess the question is, you know, I mean, with sort of a basian philosophy about any -- the interpretation of any test is really based on your pretest probability. And we're getting very confused around whether or not we're supposed to apply

the same screening approach to patients with a very high pretest probability.

And there have been some, you know, moving examples about, you know, people with Lynch Syndrome and people with, you know, multiple relatives dying of breast cancer at very young ages who the pretest probability is extraordinarily high that they have a genetic mutation that would be, it seems to me, very worth screening as opposed to sort of the population average risk where, you know, you're going to have to search of a lot of genes. They're going to all have very low post-test probabilities associated with them with the exception of rare sort of circumstances.

And so as we try and conceptually get our arms around the question before us, you know, should there be lots of filters and should we think that there would be applied lots of filters before a screening test is applied such that the post-test probability would be high that the disease is really present, or are we really opening it up to every mom and pop, you know, genetics over the web shop that

could apply and go to any patient of any risk for whom

Medicare would be stuck footing the bill?

DR. SCHEUNER: What I think we also heard that, you know, with the Mendelian disorders, again the BRC1 and 2, the Lynch Syndrome, et cetera, that what we're looking for are variations or mutations that are -- that actually are -- versus associations with markers, these SNPs.

I mean, it's really two different things. And I don't know. I think we heard from one of the speakers that perhaps we should think about it as diagnosing a hereditary syndrome when we find these mutations in the single-gene disorders even though the patient may not yet have the cancer that's associated with it and considering the others more of a screening test.

DR. RICHNER: The best way to serve CMS right now is for this very important panel to give you some ability to define screening in a way that will satisfy the Medicare restrictions that you have in terms of what that definition is.

Is there some way that we can help to define screening with your construct that would be allowed to

have sort of variations on what you can cover or not?

DR. SATYA-MURTI: Well, I think our current deliberations, with the minutes and transcript, that itself is probably one of the ways we're helping.

DR. TEUTSCH: I think that the whole issue of population is really what we're getting at the root of here. Because most preventive services are used in a way that's somehow targeted, whether it's to pediatric age groups, geriatric age groups, men, women.

As we talked about, even screening for diabetes according to the Preventive Services Task Force is based on some other characteristics that convey some level of risk that justify screening.

So if one -- it seems to me that family history really isn't any different from any of those other kinds of things that are knowable to give you some sort of opriori assessment of risk.

And the idea that it's somehow very

different strikes me as a bit strange 'cause these are

all things that are characteristics of the individual

who are otherwise asymptomatic that could tell you whether or not there is a sufficient level of risk to warrant screening.

So I think it's a question about how you just define population. We always define it. We are almost always screening in some subpopulation that we think warrants it because the benefits exceed the harms.

DR. SATYA-MURTI: Dr. Grant? -- yes. I'm sorry.

DR. HOLTZMAN: Well, I take a little exception to that, Steve, because I think then family history becomes screening test, if you will. But then the follow-ups to that, if there is a positive family history, no longer fall into the screening category. And maybe we need another category between screening and diagnostic.

But I don't think that to apply -- to skip the family history test and to begin to conclude that

screening should be applied regardless of family

history -- genetic screening be applied without a

family history when there is, for relatively low probability situations, a mistake.

There's a big difference between applying a test, a genetic test in a family that's positive for BRCA1 in terms of the predictive value of that test than there is between applying that test in the general population. And I think that that use of the prevalence of the disease is a very important distinction that one should make in defining when the test should be used as a screening test and when it should not be used as a screening test.

DR. GRANT: I don't know. I guess my feeling is we're getting a little bit hung up on trying to come to some idea about the definition as opposed to operationally what we're tasked to do.

What we're tasked to do is talk about preventive -- preventive tests. Am I correct?

UNKNOWN MALE VOICE: Yes.

DR. GRANT: In the absence of detectable or

clinically manifest disease. Now, whether we call it

-- you know, as alluded to and, you know, as clear as

the ultimate utility of any test will depend on the patient population, the prevalence of disease in which you apply it.

Whether you call it, you know, one or the other, I don't think is really the issue. I think the issue is really we're talking about preventive tests. And that's the way I would see it.

DR. GUTMAN: Yeah. I have a series of questions about the ground rules here. So am I reading this correctly that -- that before it actually fits into a decision by CMS, it does require some kind of evaluation by the U.S. Preventive Services Task Force and a determination that there's a level A or B?

Is that correct? That in the absence of that, then you don't move forward?

DR. SALIVE: Yes.

DR. GUTMAN: Okay. So that in itself rations the number of assays.

So then the second question I have is, does

that mean that the recommendation be -- by the U.S.

Task Force, that that recommendation be a screening

recommendation?

DR. SALIVE: I don't know think it would fall in any other category.

DR. GUTMAN: Okay. And then the third thing is, does the U.S. Task Force have a definition of screening? Does anybody know?

DR. SALIVE: I did try to find that. And I thought they did. But I couldn't find it in, you know, very concise --

DR. GUTMAN: It would probably be a really good idea to have that.

DR. SALIVE: I couldn't find a very concise definition. I think they have one.

DR. TEUTSCH: The Preventive Services Task Force divides their recommendations into three categories.

DR. SALIVE: Right. I know.

DR. TEUTSCH: So you can sort of think of it by exclusion.

DR. SALIVE: Right. Screening.

DR. TEUTSCH: Screening, counseling and

chemo prevention so when you're detecting something in an otherwise asymptomatic person, that's what they mean. Because counseling, yes, you could say, "Do you get physical activity?" "No." "Well, you should." That's a counseling sort of a thing. Right?

But there's a screen. But what they really mean is specifically in the circumstances where it's distinguished from counseling.

DR. SATYA-MURTI: Well, there is a glossary in the USPSTF which spells out what these recommendations are. And they do go into some detail about each of these statements, A, B, C, D. And then they have an I which means indeterminate.

So there is some verbiage there for the recommendation. And it's on their public site.

One other perspective as a former Medicare medical director is sometimes, some of these task force recommendations just cannot catch up to with what is requested at large with providers, and

providers of all stripes, physicians to laboratory.

So sometimes, the decision needs to be made,

either at the CMS level or at a local medical director level without any of these additional bulwarks of determination of recommendation. That's often the practice.

Those of us who have been out there know that. That's what I meant, that comment about science catches up with practice. And things are put into practice well ahead of any recommendation some of the times. And I'm sure this is going to happen here, too.

DR. SALIVE: I guess just to amplify in response to those questions from Dr. Gutman, I think that our focus today is on those -- you know, how would we at Medicare consider something to be reasonable and necessary in this arena for screening and prevention.

So we can sort of take off the table the Task Force gives it an A or a B. You know, they have their methods. They will evolve. I'm sure they exist

-- you know, there are articles about how that has operated in the past.

But let's focus on -- so there may be some overlap with what we would use to consider something reasonable and necessary for Medicare and what the Task Force would look at. You know, probably a large amount of overlap, I would say.

But let's discuss it, you know, specifically. And that's why we have the series of questions.

DR. DANIS: I wanted to just ask one question prompted by the case that Dr. Eng raised about someone of Medicare age who requested testing for the sake of someone younger in their family.

I just want to ask whether there is any way that -- as I take it somewhat off the table in terms of what our agenda is today. But it seems to me that one could make a case, if one is thinking about the broader issue of the well-being of that family, that it's reasonable and necessary to do some testing.

And I was -- is there any construal of the

regulations that would permit reimbursement for that,

or is that something we just cannot deal with?

DR. SALIVE: Well, I would never say never. And certainly not in this meeting. But the difficulty is that, you know, it's a health care program for the beneficiaries. And so, you know, with rare exceptions, the services are for the beneficiaries and for the treatment of them.

So you know, I really -- you know, I appreciate the example as provided by the doctor. There's some rare exceptions where we pay for services on somebody else that will benefit the beneficiary or vice versa. And I can't think of any, actually, in the vice versa category.

In the category of things for the beneficiary, you know, transplant donors are sometimes tested before a transplant. And they are certainly likely not to be in Medicare. I think that's an arena where we have some -- some, you know, example.

So that's where we are. But let's try to focus on the big picture.

DR. SATYA-MURTI: There is a provision under Medicare statute or regulations for individual

consideration. Medical directors would routinely do that after extensive case by case review. And there are several such instances. I've done some over the years.

I think, Maria, you have housekeeping announcements?

MS. ELLIS: Yes. Before we break for lunch, could you please make sure that you discard any trash, as we are not really supposed to eat or drink in the auditorium.

And also, please keep in mind any CMS guests here attending the MEDCAC, you are only allowed in the auditorium, out here in the foyer, the main lobby, the lower level lobby, and the cafeteria. And of course, you can use the restrooms which are right down the hall.

If anyone is caught anywhere other than those places, you will be asked to leave the conference, and you will be -- you will not be allowed

back here at CMS single site.

And that's it. We'll see you at twelve-

thirty?

DR. SATYA-MURTI: Yes. We have --

MS. ELLIS: We'll be back at twelve-thirty.

DR. HOLTZMAN: Can I ask you a question, one question of one of the panelists, please, before we break? Do I have your permission to ask a question?

DR. SATYA-MURTI: Thirty seconds.

DR. HOLTZMAN: The question? Yeah. It's for Dr. Wenstrup. You know, I'm very sympathetic to the notion that insurance coverage should be extended to people who are asymptomatic but who have a relative who's had a positive BRC1, BRC2 test.

But I'm interested in terms of the Medicare population in particular, you gave an example of one case. But I wonder if, in people over 65, would BRCA1, BRCA2, having survived that long, whether their prognosis is any different than other people, other women, who develop breast cancer after the age of 65.

DR. SATYA-MURTI: You do have time for

answers in the afternoon. I think we should -- we will open with your answer.

DR. WENSTRUP: Have the answer in the afternoon?

DR. SATYA-MURTI: Yes. That gives plenty of time to answer, I guess. Thank you.

(Whereupon, a lunch recess was taken.)

DR. SATYA-MURTI: We first have some questions, one left over from before lunch. And then the second segment of this session in the afternoon, before we go for voting, would be to have an internal discussion among the panelists. And there's enough time for some give and take in the first part, before the internal panel discussion starts.

I'd just like to remind that the panel this morning has identified, I think, three major issues. One is the great deal of difference, apples and oranges, et cetera, between monogenic disease and genome wide association test. So like the lawyers say, we stipulate that these two are two different animals.

And then we also talked about having a strong family history to raise the prior probability

before unleashing a test.

And the third major issue I think we identified is that there ought to be some kind of identifiable or tangible outcome benefit as a result of these tests.

So I think those three issues are very much risen as the cream of the mixture. So with that as a preface, Dr. Holtzman had a parting question, and you want to respond to that now, in addition to talking to him. Can you rephrase the question?

DR. WENSTRUP: Sure. I believe that Dr. Holtzman was asking about what the residual risk of cancer was for patients' hereditary cancer syndromes, when they reach sort of the Medicare age group. Is that a fair --

DR. HOLTZMAN: That's part of it. I think the other part of it was if you identified, say, a 65-up individual, BRCA1, BRCA2, what was the prognosis of that natural history in that woman compared to people

over that same age who did not have BRCA1, BRCA2, who developed breast cancer.

DR. WENSTRUP: Right. Some of that information was provided in the letter that we provided to the panel. But with regard to BRCA, I would refer you to a paper by Chen, published in the Journal of Clinical Oncology in 2007, that did a meta analysis of sort of the penetrance, sort of the age specific penetrance of HPOC, and found that in the 60 to 70 age group, the folks who had -- if I can quote here, I think we have it here. "A BRCA mutation carries at a 17 to 19 percent" -- according to Chen's meta analysis -- "of residual risk or for risk of developing cancer between the ages of 60 and 70." And for ovarian cancer, it was 10 to 22 percent.

DR. HOLTZMAN: What was it for breast cancer?

DR. WENSTRUP: Seventeen to nineteen percent. Again this was a meta analysis, published in JCO in 2007.

DR. HOLTZMAN: So it's much lower than in

younger women, very much lower.

DR. SCHEUNER: It's not in the ten-year

interval.

DR. SATYA-MURTI: Yeah. Over what time period is this?

DR. SCHEUNER: Age 60 to 70.

DR. WENSTRUP: Age 60 to 70.

DR. SATYA-MURTI: Oh, ten year.

DR. SPERTUS: And what's the risk for women without BRCA1 in that time period?

DR. WENSTRUP: I'd have to get back to you on that. Charis, would you happen to have those numbers?

DR. ENG: In comparison, the lifetime risk declined because they say between the ages of 25 to 80 of breast cancer in us is 13 percent lifetime versus 10 years. And for ovarian cancer, as you know the lifetime risk for us lifetime is point five to one percent. So this is huge difference.

DR. WENSTRUP: With regard to Lynch Syndrome, retro nonpolyposis colorectal cancer

syndrome, as I sort of mentioned in my remarks, the

Heather Hampel study, published in the New England

Journal of Medicine, 2005, indicated that the median age for onset of a HNPCC related cancer was 58. And there have been other estimates that actually put it slightly above that.

I don't actually know what the exact prevalence is. But you can see by the average or the median age of onset that still there is a significant amount of residual risk over the age of 65.

DR. HOLTZMAN: So you don't have data on --

DR. HENDERSON: I think there's a potential of a clinical fallacy here in thinking, which we oftentimes employ in medicine, particularly in cancer medicine. I always give two major fallacies. One is that risk justifies treatment. And secondly, if there's no risk to the treatment, you can give it to everybody. I think those frequently come into our thinking.

So you, for example, state -- well, I don't know whether it was you. But anyway in the

20 presentation for Myriad, they say proven medical

21 intervention, such as prophylactic removal of breast

tissue and ovaries can reduce the respective occurrence of cancer by over 90 percent.

However, I think most of the studies -- I didn't go back and double check these articles. I do know the original study that led to a widespread approval of BRCA1 and BRCA2 from the Mayo Clinic was a retrospective study and included patients of all ages, but particularly younger women.

So the question is, is it reasonable to assume that the effects of these therapies are going to be the same, for example, in a 40-year-old woman and a 70-year-old woman. We know that the natural history of cancers and particularly for breast cancer is long. In other words, the period in which the cancer is developing is very long.

And secondly, we know from our studies with adjuvant therapy that the reason that we had to go to adjuvant systemic therapy as opposed to things that were tried earlier including perioperative therapy and

bigger and bigger forms of local therapy, efforts not

to disrupt the tumor and so on, is that metastasis are

established some time. In fact, it may be as long as years or even decades before the diagnosis. In other words, we can see that on the basis of the outgrowth of metastasis.

And if metastasis have already been established, then, of course, these therapies will not prevent the disease and probably will have no impact on the survival. So it's plausible that the effect of an intervention on a woman who is let's say three years or two years or even eight years from expressing that disease and all of its clinical manifestations, that is, a lump in the mass, with or without other findings, would be different than for a woman who is actually being -- where there is an intervention 20 or 30 years in advance of when that would occur.

So you have to assume two things. One is that there is a risk associated with a genetic factor. And secondly, that the intervention is going to be as effective. So the question is, are there any such

data. I'm not aware of any. And I think that this is fundamental to some of the questions that we're going

to be asked to address this afternoon about whether you treat the particular population, the Medicare population, differently than you might -- usually you test differently in the Medicare population than in other populations.

So I think this is a fundamental question directly relevant to our charge today.

DR. WENSTRUP: With regard to HPOC, you're right. There isn't sort of risk stratified data on risk reduction of for, say, removal of the ovaries. But with regard to Lynch Syndrome, certainly removal of a polyp after sort of a diagnostic colonoscopy would substantially reduce risk regardless of the age.

DR. HENDERSON: Well, I was addressing this particularly to BRCA1 and BRCA2, where we have a lot of data and also to the general issue. I mean, even when you come to polyps, you've got the same problem. There you're talking about removal of something that again might not be manifest for two years or five

20 years or twenty years. We just don't know what the

21 natural history of all of these are untreated.

DR. SPERTUS: What are the prevalence of the BRCA mutations and of Lynch Syndrome in the population? We heard a nice presentation about the -- even if you had a 99 percent sensitive and 99 percent specific test, what the false-positive rate would be as a function of disease prevalence.

Can someone just illuminate what the prevalence of these mutations are, particularly in Lynch Syndrome, which we are giving a lot of attention to?

DR. ENG: Yeah. Well, since I'm up here. Well, let's go back to BRCA first. We have to walk first before we run. And I think you are supportive of that.

So the family history of cause narrows that we're not testing the general population. But I will address that. So BRCA1 and 2 in a very enriched population, so the Askanazy Jewish population, the three founder mutations, is in the one to two percent

prevalence.

We also know that for all comers of breast

cancer, it's a five to seven percent prevalence. So let's say five percent times 30 percent. So then let me tell you about the Heather Hampel study. So I was the chief of the division of human genetics when that study occurred in Columbus.

So this is a population based study of all incident invasive colon cancers in central Ohio. There were thousands. Strategy took was MSI testing on the colon cancer so that phenotype for lack of --

DR. SATYA-MURTI: Could you just speak a little closer to the microphone?

DR. ENG: Sure. Cut to the chase. All incident colon cancers, three percent risk of finding HMI mutations in the population. I mean, that's very large. So what we're actually doing at the Cleveland Clinic and actually major medical centers like Utah, Memorial, Sloan-Kettering, blah, blah, blah, is every colon cancer is subject to IHC and MSI.

And those that are positive are screened by

a genetic counselor. And of course they have a

brochure. They know a counselor's screening. They

know a counselor's going to call them. And we call them in for a genetic assessment. The uptake rate is 76 percent, which is very high.

But you see, that's a quick screen. It's cheap IHC because there's several genes versus sequencing all three genes for several thousand dollars. You pay a couple hundred, IHC, which tells you which gene to look at. And then you just sequence that one gene.

DR. TEUTSCH: Charis, while you're standing there, a couple of other questions again relative to the Medicare population, just of interest. How often is the proband actually of Medicare age patient? Aren't the families usually identified before someone in their 60s actually gets it? That's question one.

And the second question I have is that at least in breast cancer, we used the Parmigiani model or others to decide who to send for testing in our average population of younger women. By definition,

the Medicare population, you've taken out the age part

of that index. So is there a modification of those

models to decide who to test in the Medicare population, or is it just based on family history alone?

DR. ENG: So let's go to colon cancer because the population based study -- so that's the key, population based. It's not selective. So the first study are select. When you select the families get larger and larger, falsely, and the ages get lower and lower. When you use the population based study -- so the first Hampel study that was referred, the mean age of the people diagnosed with HPCC purging line mutation analysis is 58.

The validation study -- and these are prospective studies which was just presented -- the average age is 62. So that's --

DR. HAYES: So it's reasonably likely the proband would be at a Medicare age.

DR. ENG: Exactly. And that's why --

DR. HAYES: And so my second question is,

are there modified models for older patients to decide

who to get tested, like we use in, if you will,

regular -- in the younger age breast cancer patients?

DR. ENG: So we're back to breast versus colon where the only -- where the screen is MSI and IHC testing of the block.

DR. HAYES: So it's family history only?

DR. ENG: And then it goes down. So just to give you an idea. Of all colon cancers, 15 percent are going to be IHC null. And of those, then one-fifth of that will have a germ line mutation.

DR. TEUTSCH: I think there are a few points that build on what you just said. One is, of course, that the actual test in the proband doesn't do the proband any good because the --

DR. ENG: No. That's not true.

DR. TEUTSCH: Well, but it does very little good because the primary issue is to go back then and screen the others more intensively. From a prophylactic perspective, you've got to --

DR. ENG: No. In fact that's no practice.

DR. TEUTSCH: These people should be screened.

DR. ENG: No. I will be sued.

DR. TEUTSCH: May I finish? There are risks for other cancers. The point is -- we're talking about colorectal cancer now.

DR. ENG: Yes. We are, even more so.

DR. TEUTSCH: And so the point is that those people should be screened for colorectal cancer in general because that's the recommendation in this age group. And the question is, what's the incremental value of knowing that they have HNPCC, that means that you should then screen them more frequently.

DR. ENG: Yes.

DR. TEUTSCH: And to my knowledge, that's got to be a fairly small number. I haven't seen a study that actually does that. But one could model that out. The primary benefit is going to be to the younger people who would not normally be screened because we're talking about screening tests now.

And the incremental benefit of people who

would ordinarily not be screened who are younger and, therefore, but are at high risk.

DR. ENG: No. No.

DR. TEUTSCH: Now the natural history of HNPCC, as I understand it from Lynch Syndrome, is actually a more benign course for the colon cancer than other kinds of colorectal cancer so that the -- and again, we can go back. I'm relying on memory from the recent report from EGAPP that basically says that because the course is slower, you presumably don't have to screen them quite as often. And these people should be screened anyway.

Now, there are other kinds of cancer, as you said. There's endometrial and other kinds of cancer. And that's a different issue as to how you're going to pursue those.

DR. ENG: Please allow me. So the screening guidelines is one baseline of 50 years old for most of us, hopefully most of you don't have a germline mutation. And the next one is at 60, so every 10 years. So with the identification of a germline

mutation, the colonoscopy recommendation is annually.

Why is that?

In -- actually, when it was original study, he said, "Unlike" quote "sporadic colonic polyps, the transformation rate of polyp to cancer is extremely fast because of mismatched repair." However, this is a bit illogical, but I think it's true. An S mismatched repair gets worse and worse and genomic instability goes worse and worse. So it's a very quick transformation. And then the prognosis is sort of left alone.

So let me give you another little thing. There are now several studies that have confirmed that if you have whether germline or somatic alterations in mismatched repair, so lack of mismatched repair, you should in fact not use 5FU containing chemotherapy.

While disease free survival is not affected, overall survival goes down. The investigators from many studies believe that's because of toxicity. Although, I think the older you are, the toxicity is worse. And we'll get more and more back.

Same with BRCA1, 2 mutations; these things

in phase one and two trials. But when the woman has

metastatic disease or even if you're thinking of --the standard chemotherapy does not work very well. And you'll see this, it's sort of this response, and then it just creeps back out.

Things like POP inhibitors that seek out genomic damage or lack of repair are showing extremely good promise, even in BRCA related metastatic ovarian and pancreatic cancers. So now we're sort of creeping into it also in forms of therapeutic choice.

DR. DANIS: Can I just ask you, are our questions or the example of BRCA1 testing and testing for Lynch really germane to the discussion about screening if you would do the testing for Lynch Syndrome in someone who has colon cancer?

I mean it seems to me that this is not necessarily of a worry to us because someone who's got colon cancer deserves to have that kind of testing. We're not talking about screening at this point.

DR. ENG: But you are in the linchpin case

that I showed you where the person's in obligate care,

has no signs of the disease and these to affect it.

So that will affect his screening 'cause he still has his colon with him. And if it were a woman, it would affect the endometrium and the ovarian as well.

DR. SATYA-MURTI: So it's usually a parent of an effective proband --

DR. ENG: Yes.

DR. SATYA-MURTI: -- as shown in your case. So that may be the difference, if someone whose child has come down with the syndrome. My question for all oncologists is simply this.

So the biologic behavior and natural history of these monogenic identified malignancies is not homogenous. Right? It seems to vary in the tissue type and responsiveness to chemotherapy. Is that correct? So not all --

DR. HAYES: That's very correct.

DR. SATYA-MURTI: Okay.

DR. HAYES: I mean that's what we're being asked to review. My understanding is we're not asking

to look at genetic tests that predict outcomes after you have cancer.

DR. SATYA-MURTI: No. No. We're not. But my own edification, so this is -- you don't lump them all as -- yes, Dr. Holtzman?

DR. HOLTZMAN: Yeah. I haven't heard a clear answer to my question about the prognosis of BRCA1, BRCA2 in -- and for HNPCC, for that matter too, in people over 65.

Now, it's interesting. One goes back and looks at the original epidemiological studies from which the discovery of BRCA1 and BRCA2 emerged is that they were limited to younger women; women who apparently did not survive until approximately the age of 65.

So the question comes up is whether if you've got a woman who's over 65 who has BRCA1, but does not have cancer, whether for some reasons that we don't yet understand, her prognosis, having survived up to that point, is going to be considerably better than in the young women who have been diagnosed

because of a history of breast cancer before age 65,

well before age 65 in their families.

And I think I've asked the same question too about HNPCC. And until we have the answers to those questions, I don't see how coverage is justified under Medicare for people 65 and over.

DR. ENG: Lynch Syndrome is relatively easy because there is a large proportion, so the data is there. There are enough people with germline mutations who are over -- half of the people are over 62. We just heard that. So they do -- now, to say that all Lynch Syndrome behaves identically is silly. But that's not possible. There's gene-gene interruption and gene environment interactions. So --

DR. HOLTZMAN: Well, let me ask you as far as HNPCC, before you go from there, because my understanding that the U.S. Preventative Services Task Force has recommended colonoscopies as a general screening technique.

DR. ENG: Right. Yep. Yep.

DR. HOLTZMAN: Now, if you've survived up

until 65, you've talked about it in younger people

doing an annual colonoscopy, which Preventative

Services Task Force does not recommend. But if you've gotten up to age 65, why isn't colonoscopy every 10 years good enough?

DR. ENG: Because the conversion of polyps to colon cancer is extremely fast with mismatched repair deficiency.

DR. HOLTZMAN: Even in women who have remained asymptomatic up to -- people up to age 65?

DR. ENG: Yes. It's penetrance. Correct. So then let me tell you one more study which I did. And so (inaudible) taught me when I was a fellow. He -- and you have not changed, by the way. He, of course said, case control studies -- you've got two prospective studies.

Now, of course, even though we're saying it's not covered, it shouldn't be covered and all that, it's even as early as 1995, as I was finishing my clinical cancer genetics fellowship at University of Cambridge, it was deemed not ethical on both sides

of the Atlantic actually to do a case control study.

I mean germline mutation -- let's just do the usual screening. Let's do the intense screening. However, before that, the Finnish -- so good for them. Albert de la Chapelle in Helsinki did a prospectus study where people had Lynch Syndrome. So there was no gene at the time, but had Lynch Syndrome, and did usual screening versus anal colonoscopy. And, of course, showed a dramatic decrease of risk from death of colon cancer.

We are seeing one and two there's less data because, of course, as you say, the cohort that's over the age of 65 is sort of shrinking.

Now, Craig asked -- I guess the reason why I first got up -- is an intervention going to be different in an old and younger woman. And one example is prophylactic TAH PSO.

We know that in people, in fact, under the age of 45, if you do a TAH PSO and BRCA germline mutation positive for people, not only does it

decrease the likelihood by 95 percent -- it's true of getting ovarian cancer -- it will actually reduce the

risk of breast cancer by 40 percent.

Now, it doesn't just drop off at 45. There's a curve. And because the older you get, well, you do decrease the ovarian cancer risk because ovarian cancer occurs later in BRCAs. It does not lower the risk of breast cancer as in a younger woman.

DR. PERFETTO: I want to follow up on Dr. Holtzman's question because I want to make sure that I'm understanding.

If someone had their colonoscopy at 50, and someone had their colonoscopy at 60, and they were asymptomatic, then what really is the probability at 65 that something changes that dramatically that this test kicks in and changes the prognosis for what percentage of patients at that age? And if something happened at 65, what's the probability that between 60 and 65 there was such a change? Do we know that?

DR. ENG: Yeah, because in Lynch Syndrome, these things really do pop very quickly. We've even

had patients who have had colonoscopy the previous

year, who had colonoscopies at the Cleveland Clinic --

good press, blah, blah, blah -- the next year there are already polyps or even insight to cancer.

DR. PERFETTO: So we know that there would be a difference in survival if someone was clear at 60 and not clear at 65?

DR. ENG: I think the Finnish study that addressed that -- and the answer is yes. Because that's the only case control where they do the population screening, which is similar to ours versus the annual in the mutation carrier. Do you know of any other, Marin?

DR. SCHROEDER: You're asking if they are clear at 50, they are clear at 60, no Lynch, nothing?

DR. PERFETTO: No Lynch. Nothing.

DR. SCHROEDER: Clear at 50, clear at 60.

DR. PERFETTO: Which is kind of like -- I mean someone would have had to be asymptomatic. We're taking about for the Medicare population. If someone will have to be asymptomatic going into the Medicare

program for this to kick in and for it to change

things dramatically --

DR. SCHEUNER: But you're also assuming that a hundred percent of people are getting colonoscopy at age 50.

DR. PERFETTO: We can't do anything about that.

DR. SCHEUNER: Well, I know. But let's also agree that a lot of folks present with their colon cancer having never had any screening test prior. And I guess the question you're asking is a good one. And that is, if you have HMPCC and you've had colonoscopy at 50, and you've had colonoscopy at 60, and no polyps were found, then what's the penetrance if you're a gene carrier at 65? I don't know that anyone's done that study.

DR. ENG: No, not that specific study. But I think you can certainly extrapolate from the Finnish studies the closest to that.

Let me tell you about another gene. It's Paragonimus. It is rarer.

DR. SATYA-MURTI: Talk into the mic.

DR. ENG: Sorry. Let me illustrate that.

So paragonimus and pheochromocytomas all come as 30 percent and have a germline mutation in one of five genes. Succinate Dehydrogenase BC and D are the most popular, followed by REC. And you will recognize that's mu2 gene, but of course, and VHL, the Von-Hippel Lindau gene.

SDHB has such -- it has a funny penetrance. And in some individuals, they are clean and can pop a paraganglioma at 70. So, yes. I'd like to understand penetrance. I think every geneticist does because that's the magic. Even better, I'd like to say -- I mean we say -- okay, the gene I discovered, P10, which gives a risk of breast and endometrial cancer.

I can say you have a germline P10 mutation. You're at 50 percent lifetime risk. But which 50 percent are you? If only we had that.

DR. SATYA-MURTI: Beyond these three triad of threats we've talked about, are the panelists concerned or have any questions outside, in a more

encompassing fashion, outside of these three tumor types we've been talking about?

DR. SPERTUS: Well, I remain concerned about the translation of knowledge in the practice. So I think that's a really big issue. I don't think that we have a physician work force or the capability to integrate genetic variants into multi-variable risk models and to be able to interpret and counsel patients appropriately. So I'm very concerned about how this would be applied.

And, you know, something I haven't articulated is I still have concerns about the diagnostic accuracy of the tests. And I think that we've done a fair bit of genetic research in cardiology. And we had a situation where one extremely good group was using Sequenom to look at a bunch of genetic polymorphisms. Another group was using pyrosequencing that was equally competent.

There were a large number of discrepancies between the same genes in the exact same patients that needed reconciliation. And so, you know, I don't know

how we're going to really create the CLIA type

standards to be sure that what we say somebody has is

what they have. And what they do in Cleveland Clinic may not be what they can do in Kansas City.

And I don't -- I still have concerns even about that level of -- I mean we're just presuming that we can somehow make the diagnosis very accurately now. And I would put to you that that's not clearly, at least in my limited experience, always true.

DR. SATYA-MURTI: Your misgiving applies to these three: Breast, Lynch Syndromes or --

DR. SPERTUS: Oh, I thought you meant, was I concerned about -- I thought you were raising three issues that came up earlier. I was just trying -- I mean, I think that you can get your cardiovascular risk profile on the web. And that's very worrisome to me. I mean we haven't talked about cardiovascular disease, but that's a huge problem. And there are people going around, feeling unnecessary comfort that they aren't at risk for cardiovascular disease. And there are people with a lot of anxiety that they have

it, even though they don't.

And so I think that it's a very befuddling

area to zero in on these very specific single gene mutations and very mortal diseases is a little unfair, given that a broad coverage decision would apply to many more diseases including multigenic diseases for which there are very few, very strong penetrant common risk factors that are strongly associated with disease and outcome.

DR. SATYA-MURTI: Yes. That's also exactly where I'm going. We seem to be bifurcating into lots of very specific questions about these three defined syndromes and neoplasia. But we're also trying to apply comparable standards to many other genetic tests.

So should we preface each of our thoughts, make our thought process summaries, to which one are we talking about, all genetic screening or only these three?

DR. SPERTUS: Well, I would just think that if we couldn't reach consensus that it's worth it in

these specific scenarios, then it clearly would not be

appropriate in these more complex multi-genous

species.

DR. GRANT: Actually, this discussion is fascinating. But if I'm not mistaken, our task is really to address the broader issues of evidence surrounding genetic testing for preventive purposes. And from that perspective, this is very useful and instructive, in terms of identifying some of the issues involved. But I think to focus in on them at much greater length from just where I sit -- I mean, I know something about a little bit of everything, but a lot about all things.

So I would -- I think that the take home for me is, first of all, there are tremendous numbers of uncertainties involved in evidence in terms of how it fits in an analytic and a decision framework and how we apply it to a Medicare population, with a Medicare population being 65 plus or younger. And to me that's where maybe I would like to sort of invest our efforts a little bit more.

MS. DAVENPORT-ENNIS: And I just wanted to make a couple of questions to my colleagues on the

panel.

I think for us in the patient community, there are two things that the BRCA1 and BRCA2 and of the Lynch test clearly have affirmed to us. As we have moved those genetic tests into a broader population in the United States, indeed there have been therapeutic interventions that have prevented development of disease. And there are people today in the United States who are benefitting, as are their families, because of that interventions.

I think on a global level, for the patient community, I think what genetic tests do as screening tools, is to provide an opportunity for hope. I feel this panel, to your point, is here today to deal specifically with screening genetic tests as they relate to our ability to employ prevention processes.

And I think for patients, I would urge the consideration that any decision that we make in this room today will indeed impact decisions that are being

made by payers across all populations of this country.

So while we may be here working with CMS and working

to try to make a good decision for that population, let me remind you that for the population we serve. Forty-four percent of our Medicare patients are there because of disability and not age.

So there's a real need to closely examine the Medicare population. It is aged and disabled. And the real need to also understand the implication of our decision to the broader United States of America.

DR. SATYA-MURTI: Anything else? This is perceived as stillness. Anybody else wants to express?

DR. SPERTUS: Well, I mean we're all trying to be very patient-centered. Nobody's, you know, trying to -- you can say that a lot of people have been prevented. And I think in this scenario, there are. There are a lot of people, a lot of women walking around with double mastectomies that never would have had cancer. And, you know, there are risks

associated with both sides.

And if you unleash a -- and I don't mean

unleash, like I'm so biased about it. But if you start, you know, allowing a lot of genetic testing, misinformation will come, and people will make bad decisions that will hurt their long-term health because the field isn't mature enough to know exactly how to use it to best tailor therapy to the individual patient. And that's what we're struggling with.

I think that there are some terrific examples. We've heard great presentations about diseases where it would alter management and hopefully be a benefit to patients. But, you know, there's fear and there's concerns and there's test mistakes. And there are a lot of things that may make this too premature to start covering broadly, when it's done in every clinic, and every doc just sends the test off, and then has to work with it and counsel their patients.

These are the challenges we're trying to reconcile. And it's not that we're not valuing the

patients and trying very hard to do the right thing for patients. We absolutely are. And I'm just

thinking and worried about the iatrogenesis rather than the patient benefit. And it cuts both ways.

MS. DAVENPORT-ENNIS: Could agree with you completely. I think the patient community is also concerned that as we consider where we're going to go, moving forward with the decisions we make this afternoon, what's the opportunity for genuine improvement to their lives if they have the screening genetic tests. Is there going to be any therapeutic intervention that's going to stand behind that once they know what the answer is?

And from the patient population that we represent, I think there is great fear for implications of the testing to other generations within their own family. And I think there's also a reality that while genetic testing holds great promise and great hope, there also will be a financial investment to be made, not only by our government, and not only by their stakeholders, but also by every

patient who participates and then is participating in their out-of-pocket share to the process.

DR. TEUTSCH: One of the tools that we've actually found very helpful to lay this out for folks is what we've been calling outcome tables where basically you take a known population of whatever risk category, age group, or whatever, and actually begin to lay out the consequences of screening in terms of who'll be fine, the number of false-positives, true-positives, so forth. What is likely to be the outcomes of treatment? What are the harms that are likely to ensue numerically?

So they can say, gee, I have a group of a certain size. These are the likely consequences overall. So that you can begin to then have a discussion about what the trade-offs are likely to be. And it's also informative to say, gee, sometimes you need -- the issue isn't about the effectiveness of the screening test, it's about the effectiveness of therapies and the fact that you may have good alternatives.

So some of these tools I think could be really valuable for CMS as to others as to actually

lay out these things in a scenario that's a little easier to understand and, I think, for us to get our heads around than some of what we often see, which are relative risk reductions and things like that, which can sound large because you can have a high relative risk, but it may not affect a whole lot of folks.

And this was the issue we were talking about earlier and, I think, the decline rate on some of the testing on ovarian cancer screening. It's not that finding it earlier wouldn't be necessarily a good thing. The problem is you find so many false-positives who have invasive tests.

And when people start seeing that, then they sort of say, gee, I can now begin to compare some of the potential benefits which aren't really well established to harms which you can begin to understand. And that's the issue with screening is to understand those trade offs.

DR. HOLTZMAN: Well, again, I come back to

this point about how much do we know about the

prognosis of these disorders for which genetic

screening is possible over the age of 65. And let me suggest a sort of simple test, at least for HNPCC.

I mean, if you took every person who had a colonoscopy, every person who had a colonoscopy, between age 60 or 70 or pinpoint it to age 65, Medicare eligible and determined what proportion of those people had HNPCC positive mutations. And you said you would say that you were just going to do a polypectomy, what would the difference in prognosis be?

I mean I'm suggesting that as a very crude, but relatively easy measure of finding out whether there is evidence that this population should be handled differently. And that's the kind of thing -- I mean we don't have those things, as far as I know.

DR. SATYA-MURTI: It's interesting that even in these three best identified examples of genetic testing, many of you have brought up gaps and deficiencies about why someone turns colonic neoplasia

over a space of 12 months and what's the ultimate

natural history and so on. So if these best examples

of genetic testing raise this many issues, we shouldn't even be handling any of the other risk factors such as with cardiovascular and so on.

We are grappling with -- as I say, you've repeatedly shown there are statistics and data, and even there we have some questions.

DR. HOLTZMAN: Well, all I'm saying is that for a disorder, colon cancer, that we have an alternative test, that we don't yet know what increment we're gaining by adding a genetic test on top of that, in a population of 65 and over.

DR. ENG: Again I point you to the Albert de la Chapelle study where it's exactly a randomized study to exactly population type screening and annual screening. And they showed risk of death from colon cancer going down at every age group. And then after that --

DR. HOLTZMAN: Excuse me. I don't think I got it. Go ahead.

DR. ENG: So the study that I keep referring to is the only case controlled study of people with

Lynch Syndrome, who are randomized to population screening and to HNPCC high risk screening.

DR. HOLTZMAN: At what age?

DR. ENG: All ages, throughout, long study.

DR. HOLTZMAN: So the majority would be under 65. What's the number of people 65 and over who you included in that study?

DR. ENG: It's not I. This was done by Albert de la Chapelle.

DR. HOLTZMAN: I think that's a critical question.

DR. ENG: Don't remember, but it was enough. Remember, I keep saying this too: The mean age at diagnosis in the population-based study from central Ohio and Finland, identical, is 58 in the first study, 62 in the validation study.

And one other thing I forgot to tell you, that knowing these mutations -- let's say you know the person has a mutation. We heard that almost half the

Medicare population is not 65. It's under 65.

DR. HOLTZMAN: No. No. That's a very high

figure in her population base.

DR. ENG: Oh, your population. I see. I thought that was really high. I said, I didn't know that. Okay. Let's go back to Lynch Syndrome. Let's say I'm a spored case of colon cancer; stage 2, stage 3, stage 1, doesn't matter. Usually a heme-collecting will be done, with or without adjuvant depending on what stage.

If the person had a germline mutation, the recommendation is a total colectomy. Why? Because the data shows that the risk of metachronous second primaries, third primaries, is 40 percent. It's probably higher. That's an underestimate. And so the standard of care per many guidelines as well that has been adopted is a total colectomy.

Indeed, if you are a woman carrying this mutation, the guidelines suggest that when you go in for your total colectomy, a GYN oncologist should come in and do a THBSO.

DR. HOLTZMAN: But I think you need that data on an age-specific basis. I'd like to know what

that risk is at 30, 35, 40, 45, 50, et cetera, et cetera. And I don't think it's going to be the same.

DR. SPERTUS: I'd also say it seems like we're confusing two issues. I mean, once you have the diagnosis, using genetic information to plan your therapeutic approach is a very different application and screening. And so I think that the insight that you can provide from your genetic testing, how it would alter adjuvant chemotherapy, how it would alter a surgical approach, are brilliant insights in evolutions and care that we ought to be doing.

However, whether to be screening people as Dr. Holtzman keeps bringing up or even their offspring, which actually wouldn't be Medicare because they'd presumably be 20 or more years younger and would be in some other health care system, unless we do extend Medicare to all people.

But, you know, is it going to be relevant to this issue, which is really a challenging one. I

mean, we want to believe that the value of this in

screening and identifying and altering the management

and capturing people at a more curable stage of the disease. But you do need to know the incremental advantage of the screening test over and above everything else.

I mean you got their family history. You got their first two colonoscopies. And with that background information, are you going to gain a whole bunch more knowing that they're a carrier of a germline mutation that puts them at risk for colorectal cancer or not.

And we can posit that. But I think that availability of evidence to define that incremental gain in knowledge so that we can best justify screening all the Medicare population is what we're really struggling with.

And, you know, it is clearly prevalent among the numerator of cases that have colon cancer, but among all people, many of whom will never develop colon cancer after 65. It's just that's what we're

20 struggling with. We just don't know.

21 DR. SCHEUNER: But are we -- I want to make

sure I understand what you're saying. We're not recommending that the general population be screened for HNPCC. What the recommendations say is that HNPCC testing in someone who has not had a cancer goes back to the family history. In other words, you have a family history risk factor, and that's what targets you for that potential HNPCC diagnosis.

DR. ENG: Correct.

DR. SPERTUS: And what's the prevalence in those people?

DR. SCHEUNER: What's the prevalence of HNPCC in people with a strong family history of colon cancer?

DR. SPERTUS: No. Well, that's wrong. Don't keep tilting the table. Whatever the screening you're going to apply to ordering the test, that's the population we want to know about.

DR. SCHEUNER: So there's two approaches.

DR. SPERTUS: So if you're going to say

people with family history, it should be family

history. Only people with more than two relatives

below the age of 40 that have colon cancer, then that's a different --

DR. SCHEUNER: Right. So that's exactly the type of guidelines. It actually does more than just say you have a positive family history of cancer, therefore you should be screened for that hereditary form of cancer. Well, no one would even begin to suggest that. It's like the USPSTF recommendation about BRCA1 and 2 in asymptomatic women. Yeah. You have multiple family history criteria. It's not just you have a relative with breast cancer. It's actually a more stratified risk approach.

DR. SATYA-MURTI: We have some questions on this side of the aisle, too, imaginary aisle on the left side. So after you, jumping over to this side. Please go ahead and finish.

DR. SCHEUNER: Well, I guess I'm done. I'm just saying that, again, what we're talking about, the person who hasn't had cancer, and when it's a

mendelian disorder, whether it's a long QT syndrome,

hereditary cardiomyopathy, hereditary cancer syndrome,

the approach is always around finding -- the approach is generally around a high risk family history. And it's not just positive-negative. It's actually recognizing patterns in the family.

DR. SATYA-MURTI: That's a necessary prelude.

DR. SCHEUNER: Yes.

DR. GRANT: If I could take a stab once more? What's of interest here -- and it's very poignant -- is is that uncertainties are myriad. There are lots of things we don't know. But to start with, I mean as EEF does, as USPSTF does, decisions are never simple. There's some analytical framework that's incorporated with some decision model to make decisions.

And you have to fill in all kinds of pieces of the puzzle. It might be this one. It might be that one. And some of them you know. Some of them you don't know. And I think this is instructive from

that perspective to demonstrate how difficult it might

be for the Medicare population, how difficult it might

be in genetic testing.

But nevertheless, that really is the issue. And I think if we sit here focusing on this parameter or that parameter or the sensitivity, the specificity to the false-negative, false-positive, and never get to talk about what are the outcomes that are valued and how do we put all these pieces together.

And, for example, you know why is this evidence -- is this evidence different? And how are we going to piece it together? How are we going to suggest to Medicare to say derive some decision certainty about it. What is that decision certainty? I guess for me that would be very valuable.

DR. SATYA-MURTI: So yours is really the very first question, how is this any different from any other testing methodology we employ. So with probably family history and the definition of the disease is a lot more important than many of the other tests, non-genetic tests.

DR. HAYES: So I would argue -- several people have said this -- but context is important for

any test. And I think that's true here. So I find it hard for us to discuss genetic test on all of medicine, when I'm talking perhaps about a genetic test to determine whether a BRCA blend patient should or should not have a mastectomy. And he's talking about whether a patient should or should not have lipid screening or something.

DR. SATYA-MURTI: So by context, you mean you need to really individualize the tests.

DR. HAYES: So Doctor, I mean I think it's wise and good for CMS to have criteria for what they want to approve for any test, but then within that there have to be contexts for that specific test. It's true in all of medicine. I mean, I don't order a PET scan on someone who's never had breast cancer, so on and so forth.

DR. SATYA-MURTI: So you think it's even possible for us to come to any consensus, relative consensus, without context being a very important

part. Is this just not going to be outside of a specific context? It's just premature to consider all

of them together? Was that --

DR. HAYES: Yeah.

DR. TEUTSCH: Yeah. I'd like to talk about three different kinds of evidence here. One is sort of the context-free evidence. And that's the key part that we need to start with.

Context-free evidence is what do we know about the incremental value in terms of health outcomes of using a genetic test for screening compared to alternatives. That's sort of the objective information. And then can we identify a population or a group for whom there would be a net benefit?

Then there's a series of contextual issues. Some of them are what we would call social science and their context sensitive information -- and you can know that, too -- like cost-effectiveness and things like that. You can determine societal values and things like that.

And then there are things that are purely

colloquial, that are about the individual or pressure

groups or all other kinds of things. That's all kind of evidence that's used for making a decision.

But I think what we need to first help straighten out is what is the incremental value, that context-free information, that basically says can we identify a group for which this provides an incremental net health benefit based on some general values. And then you can bring in some of the social and other kinds of contextual informations that would deal with various other things.

And it's not that those aren't relevant. They absolutely are. And as you get to the individual, they can become paramount. But the point is, I think first we've got to get the science straight. So that when we consider these tests, we can say this is what we know about the benefits. These are what we know about the harms.

Or if we're uncertain, so that we can then -- and before we proceed with making general

recommendations for things that are going to be used

at a population level, the bar should be pretty high,

that we're pretty certain that there is going to be a net health benefit to the people in a specific group for whom we are going to be applying that test.

DR. SATYA-MURTI: So you envision a hierarchy where the overriding concern is context insensitive or context-free decision making. And then we zoom down further to specific disease test association and then to individual groups.

Is that correct to paraphrase you that way?

DR. TEUTSCH: Right. And you know you can see this -- I mean the paper, I think, that lays this out best is Lomas, with the Canadian Center for Health Services Research, who really talks about this as a general framework for decision making.

But I think where the Youth Preventive Service Task Force and EGAPP are working, they're saying, you know, we've got to get that right. Because first, we need to have moderate certainty that there is a moderate net benefit. If we can't get that

far, then we're uncertain and probably isn't ready for coverage decisions.

But if once you're that far, then you can talk about, gee, are people going to accept it? Is it going to be cost-effective? And those are another set of questions.

DR. SATYA-MURTI: Yeah.

DR. TEUTSCH: So you can tier it.

DR. SATYA-MURTI: Dr. Holtzman, just a minute. So we have at this juncture, before we segue to what we're already doing, internal panel discussion, is there anything else for the presenters, any other questions amongst the panelists?

If there isn't, we will continue this line of discussion for a little while longer and then move onto voting part.

DR. HOLTZMAN: Okay. Well, Dr. Teutsch just mentioned I think a very key word that we have to emphasize, and that's net; net incremental value. Dr. Grant, I guess it was, who said well, let's think -- forget about the sensitivity and specificity and think

about outcomes.

Well, there are two classes of patients who

will be influenced in terms of outcomes. Those are the true-positives and the false-positives. And we're only going to find out about the relative proportion of the two if we know something about clinical sensitivity and particularly specificity.

So I think again in particular when we're dealing with screening, as I've defined it before as a search in the population where most of the people will not have the disease in question, that the problem of what harm you do by treating false-positives is very important in determining the net incremental value.

DR. GRANT: Since I was addressed, I wasn't alluding to we should forget about sensitivity and specificity at all. What I was referring to is the sensitivity of the specific disease. You know, obviously, false-positives and false-negatives are critical to being able to determine that benefit. They drive it, among other things. So just to correct that. Okay?

DR. WEINER: I have been somewhat quiet, because although I'm a public health professor, I know

a lot about screening; I know nothing about genetics. So that's sometimes helpful, perhaps. And I'm trying to understand as someone who knows something about screening what's different here. And I get it that the family history is an important factor on the risk side. And family benefit is an important factor on the outcome side.

Otherwise, I'm a little confused. Steven, what you said was right on target. Going back to page six, the MIPPA 101 says that we can't pay for anything at CMS unless it's recommended with a grade A or grade B by the U.S. Preventative Task Force. So the other two bullets are where we are today, I think.

It's reasonable and necessary for the prevention or early detection of an illness or disability. So we're back to the prevention or early detection. And so we have to make sure that we answer the question that we focus on that. Tony, you said that several times.

And then also, appropriate for the person eligible. But I'm confused that we've been talking

about the second bullet, but that's not our charge. The second bullet, meaning the screening test meets the first criteria that you mentioned.

And then moreover in reading the questions, it says nothing about a specific test. So we're not allowed to talk about a specific test. We have to talk generically. Yet, I understand that we're being informed by the three tests that we have most information on.

DR. SATYA-MURTI: Good point.

DR. WEINER: You'll have to be a magician to bring us to the next step where we can vote on something that we understand. But you're very good, I know.

DR. SATYA-MURTI: So this is a good point. So what you're stating is let's not even talk about any of the others, except those that carry A and B. That's a sub-selecting process, so we could have been done with that three hours ago.

DR. WEINER: If that's the law. On the other hand, I have been on many of these, and we

sometimes tell them the law may be wrong at times.

DR. SATYA-MURTI: I don't know that we are not allowed to talk about it. I think we came to this conclusion as capsulized by you only because we spoke so much about all of the others. So it's like the family circus cartoon. We wandered all around and then came down to this point.

DR. GUTMAN: So I actually think that the specific discussion has been quite instructive 'cause I would argue that the questions have been put on the table, and that they translate from these examples to any examples that you would put on the table. And the questions as I read them, coming from Dr. Holtzman, is first does the test make a difference. And two, where's the beef? And three, is the beef in patients who are older than 65 or not?

I think whether it's a genetic test or a non-genetic test; I think whether it's a screening test or a diagnostic test or a monitoring test; you

can't escape those three questions.

DR. SATYA-MURTI: Well, as far as those

three questions go, Jeff, are they and/or one of the three? I thought it was and. Correct? So it's all three in your -- okay. So that's also important because sometimes some of the language is written and/or one of these three. So all these three must be met, these three criteria.

And it says it is recommended, so I know you mentioned it must be. Again, I think that we're hair splitting here, but it is recommended.

DR. SALIVE: It's in our regulations, written slightly differently from here. But it must meet all three. And as I said earlier this morning, though, I think there's definitely some overlap between how the task force reviews things and how we review for reasonable and necessary. So we're asking really your general advice on these questions. And thanks for restating that. I like especially, where's the beef?

DR. GUTMAN: There are actually six

questions on the table. And the three you just

covered weren't where I was trying to go. So I'm

assuming that you've met the U.S. Task Force requirements and that CMS is asking for advice on what to do after you've met them. Or if they decide to disregard that as a requirement, that they're asking us what to do to say something is reasonable and necessary or necessary and reasonable.

And I'm suggesting that for the individual issue that does it make a difference? And that difference might be different for lipids and for brain cancer. And then two, is there data to support that difference? And three, is that data in patients over the age of 65? I guess in terms of what makes a difference, there is opportunities for risk benefit analysis, opportunities for cost effectiveness or cost utility.

There are lots of opportunities for your threshold of what is a meaningful difference. I'm assuming you're not asking us to answer that generically for all tests. That would be quite a

trick.

DR. SCHEUNER: And maybe could we also just

think of the population as yes, the majority is over 65, but not the entire Medicare population. So there may be some individuals for whom, if we just continue to talk about over 65, they'll fall through the cracks. I just want to make that comment. I think it was brought up earlier as well.

DR. HENDERSON: I think the difference -- one of the big differences pertaining to the task force and Medicare -- and I don't know that I'm saying anything new that hasn't already been said today, but I think it's something we have to keep emphasizing. And that is, the task force says to say, here are the data that are available, and here's how they can be interpreted. As opposed to Medicare, which has to say specifically, are there data, an adequate data to draw any conclusions in patients 65 and older or in the Medicare population, if you want to broaden that a little bit?

And one of the things that's striking in

20 almost all of these studies that have been done in the

21 past, not just those that are genetic in nature, but

in general, is the paucity of data for patients over age 65. I don't know about cardiology -- those of you who are cardiologists can correct me -- but in oncology, the evidence is overwhelming that the disease increases in incidents rather substantially throughout life, including well beyond 80.

And yet, the percentage of patients or the number of patients who are enrolled in properly controlled trials goes down. And it goes down very strikingly after the age of 65 and particularly after the age of 70. So, for example, in randomized trials of adjuvant therapy, out of 10,000 patients, you may have 150 or 200 that are over age 70.

And yet we draw sweeping conclusions about the use of these therapies or have in the past in women 70 and over, with no evidence. And I don't think that this is the kind of challenge that the task force has really taken up, I don't think. It's something -- when it comes to mammography, it's clear

-- I can't remember whether the hip trial stratified or not. I don't believe that they did. I think the

over and under age 50 was entirely post hoc. And it has taken us many decades to sort out. And I don't think we've even yet sorted out completely the issue of mammography, which is definitely a screening evaluation, if not genetic, and age.

But there is clearly a very, very important age factor on what happens with the case of mammography. Mammograms become a more effective tool as the patient gets older, rather than less effective tool. But age is an important factor, which is a point that we've made over and over again. But which way it's going to cut is not something we can predict a priori. And the particular challenge for Medicare is so often they are drawing sweeping conclusions about an older population, without any data from that -- or very little data from that population at all.

DR. SATYA-MURTI: This is true with most MEDCAC meetings. Towards the end we always ask is this applicable to Medicare with the co-morbidities

and poly-pharmacy of Medicare-age patients.

If I recall correctly, the task force has

very few, if any, Grade A and some Grade B. So really, if we were to stick to the language here and be very observant of that, it only brings us down to about two or three tasks. Those who are familiar with the task force more than I, would you all agree that's like only two diseases or three?

DR. TEUTSCH: There are actually quite a few. There are a couple things. First of all, there are lots of these things that do apply to the older population that are -- because certainly most of the cardiovascular screening tests applied.

UNKNOWN MALE VOICE: Genetic tests.

DR. TEUTSCH: Well, but we've only looked at two genetic tests now. I think there are a couple of problems with that. One is the U.S. Preventative Service Task Force is gearing away from doing a lot of genetic tests. They hope I think EGAPP will do a lot of those. And that's not included in the legislation currently. That's an issue.

Also conspicuously absent from the language in the MIPPA law is immunizations, which are not

included in preventive services that are under this umbrella. But a couple of things that the task force is doing should be helpful to us or to Medicare. One of which is they're finally beginning to do some modeling studies that can be used to -- they've always had criteria for extrapolation.

But now they're beginning to use actually some modeling techniques to begin to look at appropriate age cut offs and so forth. And we saw that. For those who were on the CT colonography panel, we got a chance to see some of those models actually being done by NCI in the CysNAc group.

We then began to look at what are appropriate age cut-offs for testing. And I think that kind of thing will actually allow the task force now to begin to at least make recommendations that are more applicable, even in the face of the fact that we don't have the kind of RCT data that we often would like to have.

DR. SATYA-MURTI: Dr. Scheuner, did you have a comment on the task forces recommendations?

DR. SCHEUNER: Did I?

DR. SATYA-MURTI: Yeah.

DR. SCHEUNER: Well, I thought with regards to genetics, I think we heard earlier in the presentation in the morning that we have some guidance around hemochromatosis testing and BRCA1 and 2 testing, from USPSTF. And to my knowledge, those are the only two.

DR. SATYA-MURTI: And the Lynch Syndrome?

DR. SCHEUNER: That's EGAPP. That's an EGAPP report.

DR. SATYA-MURTI: It's not income from --

DR. SCHEUNER: Not USPSTF.

DR. SATYA-MURTI: So I would ask Dr. Salive myself, should we then stick to this combination of these three and panel answer?

DR. SALIVE: Well, no. I mean I think it was said well pretty earlier, not by me, that we want advice on the evidence standards we should use for

evaluating these in the future. I think the examples provide some insight into how these tests are being

applied now. But as I said, congress can change this law, too.

I mean it may well be that, as Steve said, the task force has some things they have focused on and other things they haven't. That may evolve. Or congress may just revisit preventive services for Medicare based on some other reason.

So we would like to know what you think the evidence standard medicare should use for evaluating these tests and, in this method, as a screening method, going forward. So that's why we posed the questions as we did. The comments are quite on target, so far. And as you get to number eight, that does address this issue that we see all the time in doing coverage decisions about how does the evidence generalize to our population. Because we know we can't generate a lot of direct evidence in our population. It's a piece of the pie.

DR. DANIS: It strikes me that one way to

help us be clear in our thinking about the guidelines we're going to use would be to be consistent in our

thinking, consistent with the guidelines that we created in February for diagnostic uses of genetic testing. It seems to me one of the things that is useful in setting guidance is to have a general for those who are creating the evidence and for those who are making coverage decisions based on the evidence, that one panel after another have some kind of consistent thinking.

And while the difference today seems to me that the threshold for the solidity of the evidence should be -- we should have a higher standard. In general, what kind of evidence we use ought to be fairly similar to what we use when we talked about what we consider solid evidence.

And I just wanted to put that on the table as a strategy. Because what we generally did last time was to say, EGAPP has set a whole set of criteria for what are better levels of evidence, and we adopted it. And we could logically do the same thing today,

setting a certain threshold.

MS. RICHNER: There's more than EGAPP. I

mean, this certainly is an extremely dynamic area, first of all in evidence guidelines and development and then second of all in the genomics world. And I think it would be -- I mean as a consultative body here, that we should also consider what's been going on at ARC, what's been going -- you know, ISPOR, next week, is going to actually talking about genomics testing and setting guidelines and evidence for that.

There's a whole variety of different consensus groups that are building guidelines and thinking about this in a very meaningful way. So I just don't think -- Marcel, you're very aware of a lot of these kinds of things that are happening. I just think from my perspective here, it's how do we balance that genomic screening should be handled differently than traditional screening; and then have a dynamic response to that again, making sure that we're very involved in how this field is evolving, that we look at individual tasks on an individual basis.

I think that's what is ultimately going to have to happen here. I can't -- embracing all the big

guidelines, but then also looking at it on an individual by-case by-case process.

DR. DANIS: Let me make sure that what I'm saying is clear. I'm not saying that the scientific evidence for any particular test is judged by -- you know, it should be judged by only one, you know, group that's doing the analysis. I think that the strategy, the logic, that was used in terms of evidentiary standards for judging one test or another and whether it is ready for -- whether all the criteria are therefore saying it's worth covering, it seems to me using that kind of logic should be fairly similar from case to case.

Do you understand what I'm saying? I'm not talking about whether AHRQ's I'm not saying we should ignore the evidence collection that lots of other groups have done.

DR. SATYA-MURTI: So consistency in the criteria.

DR. TEUTSCH: It occurs to me, Dr. Salive, for guidance, that you would want to follow a lot of

the criteria that have already been articulated. You want to make sure the test could be reproducibly quantified in multiple labs with multiple methodology so that you're always getting the same answer.

You would want to understand. And I think that the idea of using outcomes table -- so you could really plot out for a thousand Medicare beneficiaries how many patients would be newly discovered that wouldn't be discovered, so you could focus on the incremental benefit of the test.

And I think that's really important because that will carry a lot of the information about the prevalence of the disease, the false-positives, the false-negatives; and to make a decision to really count out a thousand people, how many are harmed; how many are benefitted. And then once something passes those two barriers or levels, that Medicare really ought to focus a lot on how it would be translated into practice.

There are only a few Medicare approved

transplant centers, only you have to meet certain

requirements to be able to put in your ICD and have it be covered by Medicare. Similarly, you have to give some attention to the translation of this in the practice so that it is done in centers that can inform and take advantage of all the potential advantages including the reaching out and testing of relatives and family members, et cetera, so that some of the benefits in your outcomes tables that you articulate to justify covering a test can in fact happen.

So I think if you can do those three things; accurately get the test, dramatically quantify the potential benefits and harms, and then make sure you have the infrastructure in place so that if covered, it's implemented in the way you analyze it to be implemented. And then I think you could test by test go through the screening value of the different proposed things to be covered.

DR. SATYA-MURTI: We should be ready for the questions and voting pretty soon. Yes?

DR. HAYES: So if I may just raise one question, which is much more common in the cancer

arena, I think. And that is -- and Dr. Teutsch sort of raised this in his conversation this morning. And that is, do you need to do prospective trials in each case to get to an answer here? Because the point is that by the time you get the trial done, it's 10 years later, and the technology has changed to the extent that it's no longer meaningful.

And we've thought a lot about the use of archived tissues. And Dr. Eng came to present some of this with either case control or what we're beginning to call prospective retrospective studies, where you don't just pull samples out of the freezer and run them, but you actually think through the study before you pull them out of the freezer.

And in terms of the level of evidence you need -- and it seems like most of the questions you're asking us have a lot to do more with process than a specific marker, which is great. I think this is an issue of whether or not CMS is willing to accept

prospective retrospective studies using archived samples.

Now, there are pre-analytical issues that have been discussed at great length here. And for DNA, that's usually not an issue. You usually test for -- DNA's pretty tough. It's hard to do that. For RNA, it's a big issue, where the sample is archived in a way that the results you get from an archived data set are the same that you'd get from Mrs. Smith tomorrow, if you ran the same assay.

But I think these are things -- and there are publications either now or in press that are beginning to give guidance about how the design -- again I'll say prospective retrospective studies, that I think CMS might want to consider as they move forward in these sorts of deliberations.

DR. WEINER: Usually this time in the afternoon, when we're trying to find prototypes and models of blending evidence with real world payment and politics, you know, unfortunately our hands are tied, as I was alluding to before, by various

20 legislation. And unfortunately, in this health care

21 system and Medicare particularly, we're not able to

think population benefit. But there are some health systems in the world that are pretty advanced that do.

So I would ask either the panel first, then the audience, what, for example, the U.K. Nationalistic Clinical Effectiveness NICE does on this, what some of the Scandinavians do, and closer to home, Kaiser Permanente.

I'm very interested in knowing what any one of those organizations -- if someone actually knows the policy, if they're up on it.

Anybody know about that? Either the NICE or the Kaiser Permanente?

DR. SATYA-MURTI: We talked about that briefly during the break about what NICE does. I think they've been silent in this issue. Did we not talk about NICE being somewhat silent on these issues?

DR. TEUTSCH: I don't think they've taken up many of them because they're not all that prominent in their issues of concern at the moment.

MS. RICHNER: The only one that they've addressed that I know of at this date is the oncotype

for breast cancer. That was the only one. But you're right. In general, they have been silent.

DR. SATYA-MURTI: Maybe they have been burnt by the Alzheimer issue.

DR. WEINER: How about Kaiser Permanente? Anybody know? Kaiser Permanente, anybody have experience with them?

DR. SCHEUNER: Has Kaiser developed policy or tech assessment around genetic testing? Is that the question?

DR. WEINER: That's the question.

DR. SCHEUNER: Yes. They have.

DR. TEUTSCH: Tech has.

DR. WEINER: And what is their policy, Kaiser Permanente? When do or don't they cover it?

DR. SCHEUNER: Well, I think they are similar to the USPSTF recommendations with respect to BRCA1 and 2. I think they also have guidelines around, you know, most of the Mendelian stuff that

we've talked about.

I think very few -- maybe Mark could speak

to it. I don't know. But the more multiplex panels, where everything I've read, there's very limited evidence for clinical validity and utility.

DR. WEINER: Is there anything we can learn from them, do you think, that we haven't discussed already?

DR. SCHEUNER: I suppose so. Yeah.

DR. SATYA-MURTI: Mark, do you know?

DR. GRANT: I mean there are people here who know more about -- Craig and Marin, you know. We have policies on a number of tests that are not -- so a lot of the participating plans have them as well. The difficulty is we had a discussion -- it's just a little bit off the topic, is that there are no CPT codes for a lot of these.

But we have looked at a number of the policies in a less formal -- at a less formal level than as considered in one of our typical systematic review.

DR. SATYA-MURTI: One thing I do know from being associated with coverage part in Medicare is

EGAPP and others stop with recommendation; and Tech and Blue Cross also, many a time, stop with technology evaluation and a statement. But in terms of coverage and reimbursement, Medicare goes a step further because you need to answer questions in an entitlement program whether it's covered or not.

And therefore, the converse of your question, Dr. Scheuner, would be many of them are probably looking at Medicare to say, is Medicare covering? If so, maybe do that. I know that for a fact in neurologic area where I help out my academy with some policies. So often the question is, has Medicare said anything about it?

DR. GUTMAN: So you can't pretend that EGAPP isn't there. It's right on the table, and the ACCE method is a proven method. And certainly it was my sense from the February meeting that there was some notion that that was a very reasonable starting point. That was a goal standard that there might be

equivalence; maybe AHRQ has an equivalent; or maybe

Blue Cross/Blue Shield has an equivalent; or Kaiser

has an equivalent technology. And there might be shortcuts as Dan suggested. You might get your randomized clinical trial off of a very cleverly obtained bank of frozen samples.

But it just seems to me you can't push ACCE off the table. You can't push that methodology off the table. And that if we were looking for the right target, the right target is to do it right and to answer the questions that Dr. Holtzman was just asking. And just as was the case in the last meeting, there might be some circumstances where there is such compelling information that you would want to take a shortcut or be willing to take a shortcut.

So you wouldn't want to lock the process into ACCE in an inflexible malleable totality. But for God sakes, if we don't create a reasonably beacon of reason and truth in lab tests, why bother?

DR. SATYA-MURTI: Actually, by the voting process and deliberation of this panel, you might

actually end up saying, well, keep doing the kind of work you do to ACCE and just make it even better. Or

the strength of today's voting might reflect on that. Don't change anything in the recipe. Keep doing it because we like it that way.

DR. SCHEUNER: But one of the fundamental things with the ACCE framework for evaluation of genetic tests is the disorder and the setting. And that doesn't get into the acronym, but that comes first. So just -- you know, and I think we've talked about that.

DR. HOLTZMAN: Well, Dr. Gutman has emphasized the ACCE approach, and I concur with that. The problem is not entirely with the agency CMS, the agency responsible for Medicare, but with other government agencies and other government regulations.

For instance, take Myriad as a prime example. Myriad has to comply with CLIAA, but it does not have to comply with the medical device requirements under the Food, Drug, and Cosmetic Act because it's testing in one laboratory.

Now, the reason that impacts on ACCE is under CLIAA, you only have to show analytical

validity. You don't have to demonstrate clinical validity or clinical utility, as we know it. So I think if we're going to really be serious about trying to promote getting the evidence that we need to satisfy ACCE, then we have to recognize that there are shortcomings elsewhere in the government and, to the extent that we are concerned about those shortcomings, that we do something about it.

Within FDA, I think there could be a positive stimulus to getting the kinds of studies and getting more tests available as kits, which do fall under FDA's purview. If we did something or had the congress do something to apply the same kind of criteria that are used or the same regulations that are used for drugs, namely conditional, pre-market approval and apply those to kits, diagnostic kits --

in other words, you could encourage development of kits, I would think, if you gave manufacturers the opportunity to market their kits

with very, very -- and I emphasize very -- very

stringent criteria with time lines involved, for

demonstrating not only -- well, they would have to demonstrate analytical validity, but also clinical validity and clinical utility.

But until those loopholes are closed, I think we're having a very difficult time seeing the people out there develop the appropriate evidence.

DR. TEUTSCH: I'd like to follow up on what Dr. Holtzman just said because the secretary's advisor to human genetics, health, and society had a report a year old now --

UNKNOWN MALE VOICE: Speak into the mic.

DR. TEUTSCH: -- had a report a year ago on the oversight of laboratory tests, which re-emphasized very clearly what you just said and talked about what needs to be done to deal with that issue in terms of the CLIAA FDA issues, how we -- and it uses basically the same framework, looking at analytic validity, clinical validity, clinical utility. And then talks to the other point about how we're going to get them

out there and used well in terms of the translational process, clinical decisions, support systems.

So that report's out there. It was done at the request of the last secretary. And hopefully we can get some motion as we get the new administration in. But I commend it to you.

DR. SATYA-MURTI: Are we -- bringing in CLIAA requirements, are we suggesting that this is forever going to be only a plasma or serum-based test? Presumably, it could involve tissues in the future and then tissue staining and processing and measurement. So it may not be CLIAA based certified testing only in future. Is that not correct? Maybe for now it is.

DR. MANSFIELD: As far as I understand it, CLIAA certifies laboratories and not tests. And the laboratories that are certified are those that run essentially any type of human specimen for many purposes except for breath, for some reason. And I don't think that they regulate labs that do sort of entertainment gender testing. But I don't think that the deal between FDA regulation and CLIAA regulation

as CLIAA is regulating a lab, FDA is regulating a test.

If a test is developed in a lab and offered in that lab only under CLIAA's purview, they are required to have a process for analytical validation in place. They are not required to demonstrate that the test is analytically valid to any particular degree. And there is no explicit requirement for clinical validation. And in laboratories who develop these tests, sometime the clinical validation is made public, and sometimes it's not. And I think maybe that's what Dr. Holtzman was perhaps referring to.

DR. HOLTZMAN: In part. I mean you're absolutely right that they don't approve tests. However, in certifying a laboratory, a key element is there is proficiency testing. And proficiency testing does relate to specific tests. And if a lab cannot demonstrate adequate analytical validity for specific tests, then it is less likely to be certified than if it can't.

DR. MANSFIELD: Although, let me add on to

this comment. There has certainly been a lot of debate, if you've been paying attention, that genetic

testing does not have a specific proficiency testing panel assigned to it. And so the proficiency testing for genetic tests has been arguably not as robust as for other types of tests.

DR. KLEIN: So I can speak to CLIAA. First of all, there are two facets to this question. CLIAA does have burdens on clinical validity, but it's through the personnel and through the laboratory directors who are required to, for example, be pathologists or physicians who have laboratory training or PhD. directors who have board certification in certain specialties.

The other thing that the Sages Report pointed out was that most laboratories that do genetic testing, in fact, are CAP certified. And CAP does require clinical validity. Moreover, they require proficiency testing for virtually every genetic test that's commonly performed or performed with sufficient degree to set up proficiency testing.

Most laboratories would participate in proficiency testing, were it available. So I think

that we need to consider the entire paradigm here rather than simply looking at regulations that really don't -- are a bare minimum standard that have nothing to do with clinical practice.

DR. HENDERSON: I wanted to raise my hand before that last sentence. I just want to underscore that. I think that the things you are talking about are not going to incentivise people to spend $40 to $50 million, $60 million dollars. And that's actually what the budget -- I've done it, so I know. That's the minimum budget for doing the kind of studies that we're describing.

Actually, I'm doing that from -- I'm making those estimates from say a small biotech that was running very efficiently, doing phase three studies in say patients with advanced disease. So, for example, that might involve 700 to 1000 patients. The studies that we're talking about for screening are more likely to require some tens of thousands of patients. So,

for example, the prophylactic tamoxifen trial involved

14,000 patients, as I recall, and follow up of 10 to

20 years, to get the kind of evidence that we are really saying we should have.

Well, you're talking about in the hundred to two hundred million dollar plus, at a minimum. And that's still maybe a conservative estimate. There are ways in which those numbers can be brought down a great deal. But right now, our system won't handle that kind of -- even the private sector can't really handle that kind of up front capital, with that much delay in return. Ten to twenty years delay return is just not something that happens in America.

DR. DANIS: I think that it's -- the point you just made is that it takes a huge financial investment to establish the evidence we need. But I think that a countervailing bit of financial thinking that we need to bare in mind as we make up our minds about coverage is that if we argue for covering technology that has not been well tested, we're going to be investing millions of public dollars without

knowing exactly how beneficial it is.

So I don't think that the argument that

testing and generating enough evidence to be high quality -- the fact that that's expensive -- should make us nervous about just proceeding. I mean I think the diffusion of technology without evidence is in many ways even more costly.

DR. HENDERSON: Okay. So I just want to make clear that we don't have any disagreement on that. In fact, I would argue that you want to do randomized trials in almost every area of both drug development, therapeutic development and diagnostic test development and screening test development earlier, much, much earlier than we do.

But I do think we're very unrealistic, to the point of being foolish, in not recognizing that these things cost money. Now, I would go further and say that we waste enormous amount of money when we do these studies. We could do a lot of these studies for much less money. We could integrate them into the health delivery system. And I have to say the last

MEDCAC panel I was on, I was very impressed with some of the efforts that CMS is making.

I think that to the extent that it's possible to do that, CMS has been doing some very, very forward looking thinking. So I wouldn't criticize them at all. And probably much more so than private insurers have done, where there's been tremendous resistance.

But I do believe that if we would integrate some of these things at an early stage, make certain that we -- for example, we were talking about the whole business of getting family histories this morning. The hard fact is that it cost money to get that information. There's no way that we can slide over that.

But in actual fact, we continue to dream that we're going to get good family history information that we can utilize without paying anybody for it. It's part of the ticket for doing histories and physicals. It just isn't going to happen, under the pressures that doctors, practicing physicians are

under, in order to get through the number of patients per day. They're just going to delete that. They're

going to write as was described this morning, patient has a family history of diabetes. And that's your family history.

These things all cost money. Oftentimes, in so many places, too much. Some places we're not putting enough in. But I do think we could rationalize that and address that problem.

But every time there's a panel that I'm on, whether it's, you know, government panel or non-government panel, we always end it by saying, well, that's somebody else's issue. That's the FDA's issue. That's the insurer's issue. That's the university's issue. That's the NIH's issue. But everybody keeps putting if off. It's not something we really deal with very rationally as a society.

DR. GRANT: I just want to get back to some of my original points and stay away from sensitivity and specificity. If you start out with a -- as EGAPP does, and hopefully we do, and everybody -- a

decision, analytic framework, to be able to derive some certainty of benefit and weigh it against the

harms, and you could include cost if we want to, then there is an extraordinarily rational approach to study design development investment. And you only invest in those studies that inform the elements of the decision making process, where you are going to acquire benefit.

And so I think that we tend to oftentimes just sort of talk about, we need more of this. We need more evidence on that. We always need a particular study design, study versus -- and that's not the case. And, in fact, healthcare systems with constrained resources do that, take that approach. NICE does; Ontario does. They don't go out and do, you know, hundred million dollar trials, if the value of that information pales in comparison with the cost.

And I think that if we were to approach it in that way -- and I don't know where all these tests would fit in, but they'd fit in somewhere. And we would know. We would know how much it would cost to

get the information, to determine clinical utility, to go out and get it. Or decide to adopt a test because

the benefits, as we say, of adopting it now will, in fact, we think, for all level of certainty outweigh the potential harms.

Or we decide not to adopt a test because we can't get the information. But there is a rational approach. But it fits within the whole piece. You develop a decision analytic framework to which you say, what do we need to know about this decision to be able to draw conclusions about benefits and harms?

MS. RICHNER: There's some great and exciting research that's happening now at ISPOR -- again, I'm going to mention that -- which is happening next week. There are some great methodologies now that are scalable using techniques such as paging statistics, et cetera, to look at these problems that we're up against.

And I think from a manufacturer's perspective, in terms of making sure that we have nimble stones that are using databases, using

electronic -- we're on the cusp of all of that right now. And so the worry that we only have, I think, my

worry here with CMS is only that we make a decision today that would limit ourselves, given what's happening now with all these new approaches and evidence issues that were -- we just spent, we have a billion bucks now to do a comparative effectiveness. What does that look like? How are we all going to use that in the most meaningful way, to make sure that we're -- these tests are important. They're the cutting edge. We all want them. We just want to make sure we have the right tools to offer that.

So I think that's really critical that we just don't limit ourselves to EGAPP and the US Preventative Healthcare Task Force; that we use some of the private sector initiatives that are going on and really seek some more help from the outside on some of this.

DR. SATYA-MURTI: Very good. Thank you. Are we ready for the questions and voting? Minefield? Uh, yes. The first three are discussion points. And

then there are some voting questions, four and five.

Only for the voting questions, try to give a two

minute explanation or explication of why you chose to vote this way.

The panel members, many of you are familiar with that. I'm not allowed to vote. So we'll start with question one. Are there differences in the desirable characteristics of evidence about screening genetic tests versus those of screening tests in general?

I thought our bar should be higher, particularly, we ought to know about the natural history of the disease. And that the test we are doing should not be the basis of establishing that definition of that disease diagnosis.

So maybe just go down this way.

DR. DANIS: I don't think there are substantial differences in the desirable characteristics of evidence. I think the rationale for the design of scientific tests and study design, et cetera -- I think we use the same kind of

reasoning.

MS. DAVENPORT-ENNIS: And I think our

response to that question is, in a world without prejudice or exclusion, there really should not be any difference, as we look at these.

We would also like to note for the record that screening genetic tests do present more difficulty in terms of the time it takes to get the information back. We'd also like for the record to call out that both screening test and screening genetic test can imbue with them stigma and concern in a societal level. And we feel that as we look at this particular question and try to relate it to our task today, it is an area that requires much thoughtful diligence in how we will indeed move this issue forward, on behalf of patients.

DR. GRANT: I would say that in general the characteristics are similar. But one aspect that genetics poses that other tests oftentimes do not are the downstream or the potential -- my book calls spill-off effects -- to other unaffected family

members. And I think that in the making decisions about benefits and harms, that's not something we

typically would consider. In fact, I can't think usually ever consider for a task that's screening, diagnostic, whatever, for an individual patient.

DR. HAYES: Actually, I have nothing to add to the previous three speakers who said what I would have said.

DR. HENDERSON: I would say that there are no -- in a broad sense, there are no differences in the characteristics of screening genetic tests and screening tests in general. I think a footnote to that may be that -- or two points. One is that I'm talking about what we would consider the ideal characteristics of screening tests, not what we oftentimes have. Oftentimes, the data upon which we have approved things in the past, and we've even used them, is still less than ideal. And so we're talking about what the ideal situation is.

And secondly is I'd suspect that cost effectiveness is going to become increasingly more

20 important for a screening test in general and will be

21 very important for genetic tests compared to what

we've done in the past. But again, I think that's an evolution for all tests, not just really for screening tests.

DR. PUKLIN: I believe that there are no differences in the desirable characteristics of evidence about screening genetic tests versus those of screening tests in general.

MS. RICHNER: I agree with him.

DR. SCHEUNER: I think the only thing I would want to add -- and I agree with what's been said so far -- is that I'm looking at one of the characteristics being simplicity for screening tests because typically, they are done periodically over a person's lifetime. And I think a difference with genetic tests -- so you would prefer to have a simple test that can be repeated and easily accessed and so forth over a person's lifetime.

Whereas with -- we've been talking a lot about inherited genetic traits that we're trying to

assess. Really you just need to do it once in the person's lifetime. And so maybe that would be one

difference from many of the other tests that are thought about.

MS. SCHROEDER: I agree. I think they are both similar. I would have more focus on natural history. We've been hearing from the presentations today. As a newbie to the genetic world, I'm a layman. I have no idea how much importance on the natural history the family history played in this, since my area is orthopedics. And I don't really deal with that so much.

DR. SPERTUS: I don't have much more to add except that I think it's important that because these are coming along now, that there are current modes of screening and really defining the incremental advantage over these, over other tests and strategies, and weighing a lot of the downstream ramifications is really important.

DR. TEUTSCH: I see them as the same. The only thing I think I'd make clear is that family

history is simply another risk characteristic that one

would use similar to other types of descriptors in

describing the population.

DR. WEINER: Of course, by the time you're in this and this, there's not much to add. However, the family history, as you mentioned, we've got to do much better than yes, no. So the risk variables, as one of our earlier speakers said, we must put much more energy into that.

And on the outcome side, as also has been mentioned, the positive externalities spill over as economists would say, we're going to need some help from economists and ethicists and maybe secondary payers if the benefits are really on the family and not on Medicare. And that's new territory as far as I've seen.

DR. PERFETTO: Ditto. I think the other thing, too, that we've talked about today, is that when we consider this issue of family history, that probably the one thing that this group can do is make a recommendation that in this definition of screening,

where is that going to fit because it sounds like

we've been trying to wedge it into different places.

And we haven't really settled on what's going to happen there in terms of definition. And something definitely needs to be done there. And it's probably not going to be something that's going to be legislated. So I think you're going to have the burden of trying to figure that out.

DR. GUTMAN: Yeah. I think the desirable characteristics are the same and both categories are held hostage to this context of use.

DR. HOLTZMAN: Well, I would say it depends. It depends on the definition of screening. I mean in most cases, when we look at those of screening tests in general, we're talking about a population defined trait as the group in which we use screening. So that, I mean, maybe women, adult women for mammography testing, it may be men over a certain age for PSA.

But it's not based on an individual characteristic, which we sometimes have defined as genetic screening here. So that if we're including in

our definition of screening people identified by their

family history, that's quite different than genetic

screening in general, which is almost always population based. Certainly the other examples that have been given are population based.

My feeling is that that's a mistake to include in the definition of screening, people identified by family history. And I think that once you remove them from screening, there will be more possibilities for coverage under Medicare.

But if you're talking about population based screening, yes, there are other things that have been mentioned. You only screen once. There are time differences. There is stigma. There are other factors that still distinguish it from many other forms of screening, but not as drastically as if we include family based testing as part of screening.

DR. MANSFIELD: Well, as the last person, what can I add? But I would like to pick up a little bit on what Marin said.

Since most genetic tests are only run once,

even though you can't necessarily say anything about genetic screening test in general. In specific, they

need to have quite good analytical performance because you're not going to run them again. You're going to take the answer you get the first time.

And we've observed at FDA that, in fact, a lot of genetic tests, not necessarily screening tests, have a poorer analytical performance than you might expect on the surface.

DR. SATYA-MURTI: Excellent. Stay with the microphone because we're going to reverse the order so you won't be the last.

Question two: What are the desirable characteristics of evidence for determining the analytic validity of screening tests -- screening genetic tests? So again, if we could be as succinct and excellent as we did for this question, that would be great.

DR. MANSFIELD: Well, okay. I'll just turn that answer around and say I think in general I think we need to expect quite high analytical sensitivity

and specificity. And I won't go through everything I think because I'm sure other people will cover it.

But we also need to assure that all of the possible variations that we are testing for have been adequately represented in the analytical validation. We're aware that for certain types of genetic tests, the common variations are very easy to come by, and it's very easy to analytically validate. Less common variations are extremely hard. And I think ideally we'd like to have good validation for all of them.

DR. HOLTZMAN: Well, I'll begin by saying that in doing analytic validity testing that the analyte, that which is being used and being circulated, is quite well standardized. Beyond that, I think there are a number of things that have to be done. And one is sharing specimens between laboratories and also within laboratories to show that one is getting consistent results.

And probably the gold standard so far as I'm concerned is proficiency testing, blinded proficiency testing, where again one develops a standardized

analyte and circulates that among labs. And you're entitled to just a very small, if any, number of

errors.

DR. GUTMAN: Yeah. I agree with Dr. Mansfield.

DR. PERFETTO: I think we all do.

DR. WEINER: I have no comments on this one. I'll save them for question three.

DR. TEUTSCH: I don't have a whole lot to add, other than EGAPP had laid out a whole set of criteria for analytic validity. And I think that sort of talks about the set of issues that do relate to generalizability panels and doing things in multiple laboratories. So that analytic validity is known on a population basis, not just a specific laboratory.

DR. SPERTUS: You know I think if EGAPP recommendations were followed very closely, that would be good. We've had the experience again of very, very good labs getting different answers on the same patient for the same sniff. And a lot of the genetic testings are just regions of the genome. They're not

even the specific gene that we're targeting.

And so, you know, you're going to end up

with population stratification, other challenges, that are going to make it difficult to know exactly that the -- I mean that you can measure the same thing in the same way. And that that's what's really associated with the disease that you're trying to screen for. So I think that there's a lot of almost FDA type attention that has to go into being sure that a test can be done reproducibly, and that it's going to have the same clinical validity in different settings.

MS. SCHROEDER: Reducibility was mine. Being able to -- repeatability was my key point there. Repeatability was really my key.

DR. SCHEUNER: I have no additional comments.

MS. RICHNER: I've thought about this one for a little bit. And I think again I'm going to put in a plug for ISPOR. There are methodologists from around the world that have been working on this for a

long time. They are going to be presenting panels on the analytical and validity criteria. There's going

to be compendium put together, recommendations from EGAPP, from Blue Cross Blue Shield Tech, from evidence based practice reviews from around the world.

They are thinking of new approaches now that I think will be very useful for us. And I think the Cochrane report that you provided for us is hopelessly antiquated. So given that, I think it's really important that we look to the future. And that's my comment for the record.

DR. PUKLIN: It is my opinion that the desirable characteristics of evidence for determining the analytical validity of screening tests are as presented to the panel earlier in the morning and are similar to those characteristics that are used for screening tests in general.

DR. HENDERSON: I have nothing to add.

DR. HAYES: I have nothing to add, except again, concern about pre-analytical issues as well as the actual analytical issues. These are no different

than would be concern for any other test. But it's

especially true when one is developing the evidence

from archived samples that one might then apply prospectively.

A number of investigators are starting to look at candidate genes; for example, in cancer, in the cancer tissue, with the assumption that what they get would be the same as from a white cell later. And that may or may not be true. So again, these are important issues that need to be addressed before one agrees that that's really to be supported.

DR. GRANT: I have a couple of things to add, actually. One is because we've dealt with genetic testing for some time now, the evidence on analytic validity -- and maybe, I don't know if EGAPP is found differently -- but oftentimes is absence or very difficult to come by or maybe the worst case, questionable.

And there are two parts to that. One is -- actually, more than two parts. It does not obviate the need to make a decision. So that even though we

have lots of desirable characteristics of analytical

validity we'd love to see, invariably, we don't see

them. We still have to make a decision.

And the other two parts about that is I think it's a take home message is that it's how it relates to decision uncertainty as it propagates through from -- whether to assay performance all the way down to clinical utility, that it will in effect alter our decision certainty in terms of how much clinical utility there is from a particular diagnostic -- particular screening test or whatever kind of genetic test you're talking about.

At the same time, the point has been made by many people that if you do have good evidence about clinical utility, that you can somewhat realistically say that analytic validity should be there. If, in fact, the test discriminates, and you can show that you can reclassify or whatever. If you want to go along the line and reclassify, you could improve health outcomes. That in general would probably not happen if analytic validity was exceedingly poor.

So it's a hard piece of the evidence puzzle for me, for us, and that's just my take on it.

MS. DAVENPORT-ENNIS: And I think for us I'd like to pick up with the issue of clinical utility because as we looked at trying to answer the question of desirable characteristics of evidence for determining analytic validity, we came to two conclusions separate and apart from what has already been cited. And that is number one, there does have to be clinical utility that hopefully would be reflected in the twist analysis, which is time without symptoms to treatment.

We do feel that as you look at this, the evidence has to be clearly applicable across all populations in this country. And that you have enough breadth of data for each of our special populations in this country for it indeed to be relevant.

We also would like to say that in this particular area, we think validity must focus on the fact, if you're trying to apply this to a population that is over the age of 60, then false-positives have

to be seriously limited. And what we came to report is, we would recommend there be no false-positives.

We would like very little overlap in clinical outcome. And we would like to see value easily interpreted across a population.

DR. DANIS: I would second what most people said. I think it's useful in general to require standards that make it not too difficult for those who are generating the data and charging for it, to have some understandable consistent standards. And I generally think that EGAPP standards are a good basis, with a threshold being higher than for what we would do when we're testing with symptoms present.

DR. SATYA-MURTI: Very good. I have nothing to add. EGAPP seems -- EGAPP rules. Questions three A and B, perhaps we can take them together.

Beyond aspects of analytic validity, are there meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of genomic testing -- genetic testing on outcomes?

I believe the differences refers again to

screening, where it says diagnostic testing. If the

answer is yes, which I presume most of us would go

with, we are tasked with answering one, two, and three B.

Early detection of a disease in an asymptomatic person, I thought there is no difference, except the asymptomatic person should be at high risk. And we need to know what is a high risk. I'm not sure we can quantify that. But certainly family history would be one.

And the second part is early treatment of disease before signs and symptoms are apparent. This is a bit problematic, in that I would like to see RCTs on this because if the treatment is invasive and risky -- someone referred to unnecessary mastectomy, prophylactic. So that would be a problem. And without knowing the natural history, it will be hard to measure what the benefits are.

Finally, question three B: What comparative data are needed on alternative strategies for screening? Are there other simpler measurements that

will give as much information. For instance,

cardiovascular risk is anthropomorphic measurements,

waist-hip ratio or ankle-brachial index, are they going to end up giving, particularly Medicare patients, as much information as something that's laboratory based.

So if you're going to consider all genetic screening tests, you really need data if pre-existing simpler disease as in Alzheimer's, a good clinical exam, and, perhaps, a basic imaging study would give as much information as what might be derived otherwise.

So those were my concerns.

Maybe go three A and B this way now.

DR. HOLTZMAN: Can we get some clarification because the word "screening" does not appear in question there. But it's testing. We're talking about screening, though. Is that correct?

DR. SATYA-MURTI: I think that is what it was meant to be. Jeff?

DR. SALIVE: Yes.

DR. SATYA-MURTI: They both nod yes. So it's the -- yeah, between screening versus diagnostic.

Marion, do you want to go, please?

DR. DANIS: I think I would just say the difference I see with genetic screening compared to other kinds of screening tests was raised by someone else on the panel. And that is studying the ramifications, the implications for families. That isn't as much an issue as in other screening tests.

MS. DAVENPORT-ENNIS: I think we would basically have a couple of responses. First, our answer to the question is yes. And in terms of early detection of disease in an asymptomatic person, we feel that must correlate with the substantial risk of development of disease and not just to identify risk population.

In terms of early treatment of disease before signs or symptoms are apparent, we feel the presence of genes do not always mean they are going to be active. There must be a correlation with activity that suggests a near one hundred percent likelihood of

the disease occurring. Otherwise, there is a risk of treating people who would never have developed the

disease.

As we look at question three, part B, our response here is if this question is referring to alternative methods for screening such as diagnostic procedures involving radiologic mammography and other screening such as colonoscopy, then there would need to be comparative data on survival or complete remission rate for groups of patients identified by genetic tests or an alternative screen.

DR. GRANT: I'm going to answer this a little bit more broadly. I think from what I took away from this, rather than maybe being specific, is last time just allude to what I've said before. I think the issue for evidence are not -- I think all these tests, all the diseases are different.

I'm not sure we can make -- and the natural histories of these diseases, of every disease, is somewhat different. So I'm not sure I can make blanket statements about those aspects. But I think

from where I sit, the issue really is, having the

framework and the analytical framework, you know, how

the pieces of the puzzle fit together for any particular disease.

What are the outcomes? Where in the natural history of the disease are we trying to do the test? And what stage in disease we're trying to detect it? Because that ultimately informs the subsequent steps in whatever our decision that we want to make. And it allows us to put values on the outcomes, the risks and the benefits.

And so I would sort of -- I'd look at it in that broad view. And the difference here is in the part. That's also I think somewhat implicit, but in how that all fits together in terms of providing certainty with the decisions that we make.

DR. HAYES: I hesitate to say what I'm going to say because I'm new on the panel. But I've read all of these questions now, at least five times. And this one, at least eight times. I counted. And I have no idea exactly what the point of this question

is.

UNKNOWN FEMALE VOICE: Thank you for saying

that. I'm glad.

DR. HAYES: Thank you. If what you're asking is should CMS pay for any assay or any test just because it detects disease, at least, in an asymptomatic person or leads to early treatment before signs or symptoms present, the answer is, no.

If CMS is asking me should they pay for something because knowledge of that assay is known to lead to a change in management that improves outcomes in a context that we all agree, the answer to that is, yes. But these are two very separate sets of questions. We spent most of today talking about the latter. And I think most of the day we said the answer to this is -- if the question I just asked is true, does knowledge -- should you pay for something just because it allows you to detect something else? The answer is, no.

And I think PSA for screening is a great example of that. So hundreds or thousands, if not

millions of men, have had PSA testing. And several of those have had their prostate removed and/or received

radiation. In the absence of any evidence, there was an improvement in outcome. And we now have pretty good evidence that there probably wasn't. So in my opinion, CMS should not have been paying for PSA screening over the last decade to 15 years. And so that would be true. I'd apply those criteria to any test we have like that.

On the other hand, we have decades of randomized trials that have shown that mammography does improve screening. So I would say -- does improve survival. So I would say CMS should pay for mammography. And I would apply those same kinds of criteria to any test.

So if that's the question you're asking me, those are my answers. Otherwise, I'm very confused.

DR. HENDERSON: I think I was less confused before Dan talked. I would say that the answer probably is yes. But it's very difficult to generalize across the board for all potential genetic

tests, one, for early detection of disease in an asymptomatic person. I would say that -- actually,

let me make the general point first of all.

For one, two, and three B, that in all cases, there should be generation of sufficient data to know what the test does and what its effect is on survival. I think that's necessary in all three situations.

But I'm not certain, for example, in number one that there has to be an improvement in survival, from knowing the result of the test. Go back to the early days before we had the kind of data we're describing today. Because deck panels were discussing this, including the Blue Cross Blue Shield deck panel, which I sat on.

And we decided that knowing that was important enough to a woman, that to deny her that information, which might affect her lifestyle or affect how she chose to spend her life, was important enough that this should be available, even though at that point, we did not have any data yet on

prophylactic mastectomy or ovariectomy in these

patients and didn't know whether it would or would not

improve survival.

So that is an example where I think it was incumbent upon us to get the survival information. I think ideally we would have that before the initial approval process. But not necessarily to determine a priori that in all cases, a test is worth it only if you can demonstrate that this is a way of improving survival.

Then on -- on number one also, I believe that there will be much more emphasis -- and this is repeating what I said before. I think on question number one, much more emphasis on long-term cost issues. On the other hand, I don't think that issues of quality of life are probably going to be as important there.

While on number two, I do believe that a demonstration that you increase the time that a patient has without signs or symptoms may have clinic utility. The reason I state it that way is I think

different patients may have different responses to that information. But that's ultimately part of the

patient's value system, not necessarily the physician's or the health care provider.

And finally, what comparative data are needed on alternative strategies, again, I think you have to have data on the comparative effect on survival. It may be the same. But you definitely need to have that. And again in that situation, I think, unlike number two, cost again becomes relatively important. And I think we're going to put more emphasis on that in the future than we have in the past.

DR. PUKLIN: It is my opinion that there are meaningful differences in the desirable and/or necessary characteristics of evidence about the effect of genetic testing on outcomes, and they will vary. The outcomes will then become part of a patient or family group of outcomes of other diagnostic and screening tests. And so it will be one of many, and there will be variable responses or effects of the

outcomes.

And these outcomes will not only vary with

regard to early detection of disease in asymptomatic individuals, but they will also vary within the group for early treatment of disease before signs and symptoms are apparent. And they will vary among each individual and their family context, in which the data is collected.

MS. RICHNER: I'm not going to add much to this discussion. But I'm essentially saying that it's very important to look at it from a multi-factorial perspective; from the social perspective, from the burden of illness, natural history of disease; all the things that everyone has said. I have nothing else to add on this question. I think I was more confused by the question, just to Dan's point earlier.

DR. SCHEUNER: Yeah. I was a bit confused by the question. And maybe it's because when I look at early detection of disease in an asymptomatic person, when I think of the examples we've talked about, like BRCA1 and 2 testing, it's really not done

for early detection of cancer at that point in time.

It's done to stratify risk within a family. Did she

inherit the susceptibility or not? And then other screening modalities are instituted, like mammography or breast MRI, to actually detect the breast cancer at an early stage, hopefully.

So that's where I was a little bit hung up. And then the same point, number two, early treatment of disease before signs or symptoms are apparent. So I guess we're talking about chemo prevention? Is that -- or prophylactic surgery? Is that what we're talking about?

DR. SATYA-MURTI: I think so.

DR. SCHEUNER: Okay.

DR. SATYA-MURTI: Those two would be examples.

DR. SCHEUNER: Okay. And then the last one, in terms of comparative data needed, I would agree with what the original comment about is, is there any incremental value, added value. And I think with again the Mendelian disorders, the only other thing we

can look to is the family history. And then we can do

genetic testing for those Mendelian disorders to

further refine the risk in that family. Again, it's a 50/50 for first degree relatives kind of situation.

Whereas, with the multi-plex panels for cardiovascular risk, I agree. We want to see if, you know, do they add anything to the Framingham risk score, for example.

MS. SCHROEDER: I was a little -- I thought I understood the question before we got here. And then when we were listening to the different presentations today, we started going back in time, talking about early detection in siblings and, you know, it's the parent that's in the Medicare system. So we would be doing tests to check the relatives, younger relatives. So then I got confused again.

Are we still talking about the Medicare population when we're looking at these questions? But listening to the panel, I agree that yes is the answer I would go with in specific. But I don't know. I'm still hung up with what the presentations and with the

dialogue that we've had and the discussion, whether

we're still talking about the Medicare population, in

specific. Because we have branched off of that numerous times throughout the day.

So if we're staying within that paradigm, and it is specifically the Medicare population, then I agree with things that have been said. But if we're talking the younger population, then I would throw some other questions in there.

DR. SPERTUS: I might -- I think all the points have been terrific thus far. I might say that I do think there's going to be a higher threshold of evidence needed for these tests. And I sort of hesitate to say this, but I actually think you are going to need to do some randomized control trials, like Satya proposed.

And particularly because you have a real problem with lead time bias. I mean, to use observational data and to make a diagnosis of the disease that much earlier in the course of that disease than it would have presented will make it

appear that people live longer with the disease or the

cancer or whatever it is that you're screening for

than would have been evident had you waited for symptoms to occur. But yet their total duration of survival, especially depending on the toxicity of therapy given for that newly discovered disease, won't really be evident unless you do a more randomized trial with a mortality outcome.

And you know, you've spent an awful lot of money on PSAs over the years. And so I think you could dig deep and find the opportunity to get the kind of evidence you need to really understand the value of a screening test. You know, when we talk about outcomes, I also think there is -- and that's particularly problematic if you start expanding to the kids because then you might be diagnosing a high risk for cancer, you know, in a ten year old. And they're going to live for 60 years before it ever would have presented otherwise. And so you're going to have some real sort of sophisticated challenging trials and have to keep very focused on.

But I do think you're going to want to extend beyond survival to look at quality of life and

health status, particularly anxiety. I think there's going to be a lot of anxiousness and running to the ER for every stomach ache because you're concerned that might be your colon cancer sprouting up. So I'd be very concerned about that.

And it's particularly problematic in the early detection of disease in the disease before, you know, it's markedly symptomatic. And then the comparative data would be usual care. And I think you're just really going to want to define incremental value of these new screening tests with the trial.

DR. TEUTSCH: I actually don't see a whole lot of difference here between the standard recommendations for screening. Most of the things that we've talked about are really all part of that. And in the end, it all comes down to having good evidence of clinical utility that can be applied in real world situations.

And that almost always means that you've got

clinical validity and clinical -- or analytic validity

that come before them. And so that's where the focus

really needs to be and where the work needs to be, in order to get it to inform this process.

I think some of the -- there's some work that needs to be done to allow us to stage the evidence in a more rational way so that we can get the information in real time and not get bogged down frequently on questions that may be more complicated. When we have clearer information on other gaps in the evidence that you can identify and streamline the process by saying that there really is insufficient evidence without having to do all of this work.

People have already talked about the fact that it should be on an incremental basis. I think that on outcomes tables, it will allow us to look at what is currently, what the current standards are, and how the addition of the genetic tests would change the benefits, and harms are going to be really important to see what those are. And then to look at what the economic value of them is over the longer term, so

that one can assess the trade-offs and the value.

DR. WEINER: I think the answer is no, there

are no major differences, other than the ones that we've talked about. And there are a lot of frameworks that have done a very nice job of laying out how the assessments should be made, EGAPP, Preventive Task Force, NICE, HTA, a variety of different ones. So we should look at those. With them, the little footnote has been discussed, all three or four of the rounds of the differences that my accrue to the genetic information and the legal harm.

By the way, the harm is going to be just as important as the benefit. And we can't forget about that because it will probably be more people harmed than helped. So, therefore, the people helped that benefit to be -- that would be fairly significant. I know we're not allowed to talk about money at this table. But one table in the future, they will talk about money, too.

DR. PERFETTO: We're going to get there. I interpreted this question the way that Steve and

Jonathan did. And so, it's probably end of the table

bias because we've been talking about it as it's

coming this way. And our interpretation of the question was, is there a difference between genetic screening tests versus others. And I think my answer is the same as theirs is. It's no.

I think the one thing that I would add is that maybe for other tests, we haven't been as stringent about sticking to the criteria as we need to be. And so maybe the only difference would be that we have to be more stringent about sticking to all the good evidence criteria.

DR. GUTMAN: Yeah. I agree the answer is no, because of the sensitivity of genetic testing. There should be more stringency and characterizing the characteristics and would suggest that the ACCE criteria would be a reasonable starting point.

DR. HOLTZMAN: Like several other people on the panel, I'm confused by the question. I think one of the reasons I'm confused by the question is that question is semantically incomplete. Because it says

beyond aspects of analytical validity can set it

above, are there meaningful differences? Differences

from what? So I really hesitate to even answer the question. But I will.

In terms of -- and I think Marin made an interesting and important addition to the first bullet; early detection of disease or susceptibility in an asymptomatic person. Here I think it depends again on what I've harped on all day. And that is the definition of screening. Because if you're dealing with starting screening in a population, that one must use very stringent criteria because the prevalence, particularly for genetic conditions for which we can test, is going to be very low. So one has to use large numbers of people in the study and use very rigorous criteria.

So far as early treatment of the disease, assuming that you found a susceptibility, as a result of genetic screening, yeah. I think again you have to be extremely rigorous because with the exception of Mendelian disorders -- and, by the way, BRCA1 and

HNPCC testing do not satisfy the criteria of Mendelian

disorders; that you really have to mount randomized

trials or other very rigorous ways of finding out whether you're going to make a difference.

And finally for part three B, what comparative data are needed, I think it's again important. And I raised this point before, particularly for the Medicare population, that if you have an alternative test, such as colonoscopy in case of HNPCC, we have to know what incremental benefit or net incremental benefit we're going to get from a genetic screening.

DR. MANSFIELD: Okay. I don't know how I read this question, but I'll answer it anyway. So I think that the answers are yes and no. I think a lot of the genetic tests, screening tests, that we've talked about today are for cancer, in which the treatment would be to remove the affected organ, rather than -- or to give a very toxic treatment. So I think that the evidence should be quite high for a screening test validity because you're actually doing

a very drastic measure in response to that, when there

are no signs or symptoms apparent.

And I think it's also very important, especially in the Medicare population to understand the penetrance of the genetic lesion to be able to measure your response to that. If the penetrance is quite low, then it's highly likely the person's gotten that far in life, they're not going to develop the disease. And there's no point in doing anything about it.

DR. SATYA-MURTI: Teresa, do you want to give a primer on the voting process?

MS. ELLIS: For questions three -- I'm sorry. For questions four and five in voting, if you could please hold up your number so that I can see it and so that the audience can see it, I will record your scores. But also, a few minutes ago, I just passed out a pre-score -- a score sheet for questions four and five. If you could please also make sure you put your name on it, on each one, and record your scores. That way, I'll have two versions. That's it.

DR. SATYA-MURTI: All right. Question four:

For each type of outcome, how confident are you that

methodologically rigorous evidence on the outcome is sufficient to infer whether or not genetic testing, extreme genetic testing, is effective for the prevention or early detection of illness or disability?

I think this question assumes that there is good evidence on the outcome. If such exists, then how would you answer A, B, and C, additional confirmatory diagnostic procedure? It's up for voting now.

DR. HAYES: May I ask, is the point of this question, which of these endpoints would we use to make decisions? I'll say it again. This question is like, do you ride the bus? Maybe I'm not getting it. But is that the point of the question is which of these three endpoints is the one that we would -- one that we would accept as good outcome?

DR. SATYA-MURTI: Well, the way I interpreted that is, let's say you have very solid

data showing the outcome improves as a result of a testing. Would you then go ahead and do additional

diagnostic testing? And that gives you an analog scale.

DR. HAYES: That's not how I read it. I read it as if the test said that it was sufficient that there's evidence that if this test is positive, additional diagnostic procedures would be indicated. Is that enough of an endpoint for me to say, okay, I would pay for that?

Or is it only if the test scores that you improve survival by knowledge of the test. That's the only endpoint I would take. Is that the point?

DR. SALIVE: So the intervention is the screening test. And the outcome is letter A, B, or C. And --

DR. HAYES: And we have really good evidence that A is true.

DR. SALIVE: And you have strong evidence for that outcome.

DR. HAYES: Is that a good enough outcome

20 versus --

21 DR. SALIVE: What kind of confidence would

you have to use the test, to recommend the test?

DR. TEUTSCH: So the first one would functionally be because the need for an additional diagnostic procedure would suggest that it's clinically valid, but we don't have any evidence of clinical utility. Is that right? Is that how we read that?

DR. SATYA-MURTI: No. Clinical utility is present and has been demonstrated by an approved outcome.

DR. SPERTUS: None of this applies to existing tests. Right? We're not -- we're just hypothetically thinking of something in the future. You're not asking us now is there sufficient data about genetic screening tests that we would feel that it's useful for the early detection of disease, more than other tests, improving survival or improving other outcomes?

DR. SCHEUNER: But it's asking if it's --

it's saying how confident are you that

methodologically rigorous evidence on the outcome is

sufficient to infer blah, blah, blah.

DR. SPERTUS: I mean do you guys want to rewrite the question? And we'll take a quick break.

DR. SALIVE: I don't think so. I'll try to explain it one more time.

DR. SCHEUNER: I guess I have a question again. You know, are we -- I might say that there's evidence. I think it's a five for one issue and a one for others. So --

DR. SALIVE: Well, that's why we've separated it out.

DR. SCHEUNER: No, no, no. I'm saying for A --

DR. SALIVE: Depending on the test.

DR. SCHEUNER: For A, let's say I'm going to give a very high rating for hereditary breast, ovarian cancer, when that test is done in the context of a family history, especially when there's a known mutation in the family. Whereas, I would give a very

low score to some multi-plex panel for cardiovascular

risk profiling. So it's hard for me to lump all that

together and give you a number.

DR. HAYES: In other words, if you had a test that said that a 40-year-old woman really ought to have a mammogram, if she's positive for the test. But if she's negative for the test, she shouldn't really have the mammogram. So then A would be a five there. Whereas, if you have a test that shows that a 40-year-old woman ought to have lipids drawn, but lipids have no value in treating a 40-year-old woman, would you not -- I mean this question --

DR. SCHEUNER: It's very difficult.

DR. HAYES: I have to say it makes no sense.

DR. SATYA-MURTI: Let's hear the second time explanation.

DR. SALIVE: Now, I'll fall right on my sword. Well, no. I think you know, you're right. That is -- I mean this is how we wrote it, and I suppose A is problematic. But we're going to say that again, the intervention is the screening test was

done. And you have a study that was well done that shows that it impacts on outcome A. Granted that's

not very specific, but an additional test -- it influences the need for an additional test, or it influences survival is B, or it influences other patient outcomes, patient centered outcomes for C.

And so the question is --

DR. PUKLIN: If the test is accurate and highly reliable --

DR. SALIVE: How confident are you that that evidence -- okay. The evidence that it impacts this outcome, how confident are you that that is an effective preventive test or preventive intervention for early detection of this illness in question? It's very hypothetical.

DR. PUKLIN: Supposing you have a test that results -- it's a screening test with a high analytical validity. So you've made a diagnosis. Then you're supposed to ask -- answer the question, what will an additional diagnostic procedure add to the procedure. How confident are we that we want to

do an additional procedure? I think that's where the confusion arises.

DR. SATYA-MURTI: Just to preclude if you want to do any additional testing.

DR. PUKLIN: Yes. Well, if it's highly valid, it would preclude us from wanting to do another test. And if it has flaws, we might want to do something. So it might be equivocal. Which way do you go here is the question.

DR. PERFETTO: I was here for the February meeting. I think a few of us were here. I was here for the February meeting, and there were a few of us that were here for that meeting. And we had the exact same discussion about this question.

And I think in order for there to at least be some consistency between the voting that happened that day and today, if that's at all important, is that the way that Steve described it to us on that day is if all you knew was that one endpoint, how would that affect your decision making? Would you feel confident? Would that be sufficient for you? If all

you knew was about that one endpoint. Is that what

you're looking for?

DR. SALIVE: Yes.

DR. HENDERSON: Okay. So you're not -- okay. So that was 180 degrees from the way I interpreted it originally. So this is based on all hypothetical. I think you used that word. It's not based on your assessment of what the evidence is right now for any or all tests.

DR. SALIVE: Correct.

DR. HOLTZMAN: I think because of that assumption, it's an extremely loaded question. Because what we've heard today is essentially that there are no tests out there for which we can be methodologically rigorously sure that the evidence outcome is there. I would suggest -- I mean to get that on the table, that we not only vote for the three choices, A, B, and C, but we vote on the block in front of it.

How confident are we that there are methodologically rigorous evidence on the outcome

sufficient to infer whether or not screening genetic

test is effective for the prevention of early

detection of disease? And I would add only in the Medicare population, which is I think what we're charged to do.

DR. SATYA-MURTI: Well, I think he's presuming that -- stipulating there is such a test.

DR. HOLTZMAN: Well, I just -- but there isn't. I mean that's why it's such a loaded question.

DR. SALIVE: Well, you know, I accept that comment. The -- I guess the notion is, say we are faced with this scenario in a few years. Would this type of evidence be convincing to you, that it's an effective preventive intervention? I guess that's the question. And as said before, considering them in isolation, that's the maximum amount of evidence that we have.

DR. SCHEUNER: Could I ask a question?

DR. SALIVE: But you can't abstain.

DR. SCHEUNER: I'm still -- I guess I just want to -- doesn't it in part depend on how much of

the condition or disease is attributed to that test result? I mean, again, if it's a risk factor of small

effect, then it's going to get a low mark because you have to do other things in order to further understand that individual's risk for disease and what steps to take. But if it accounts for the majority of the risk in that given individual, this is where I'm struggling a bit. Because again it's the --

DR. SALIVE: So are you talking about all three questions -- all three parts or just part A?

DR. SCHEUNER: No. I guess I'm talking about -- it's going to be very hard for me to think about multi-factorial genetic testing versus --

DR. SALIVE: Because Part B says you have evidence that shows a link --

DR. SCHEUNER: Survival.

DR. SALIVE: -- between that testing, intervention and survival.

DR. SCHEUNER: Okay. Right. So part B --

DR. SALIVE: And part C is --

DR. SCHEUNER: -- might be easier for me. I

guess part A is more difficult for me because I would

say again with my example of, let's say, Lynch

Syndrome now. And I have an MSH2 mutation that was found in the sister of my patient. And we know it's deleterious, and we know it's associated with high risk for cancer. And now I test her asymptomatic sister for that specific mutation. Really, in terms of defining her risk and the decisions I'm going to make around screening, that will be the fundamental test I'm going to do.

But I wouldn't say that's the case for a genetic screening test of multiple markers that explain a portion of risk for, let's say, cardiovascular disease or asthma or whatever. To me, they're so different.

DR. SATYA-MURTI: Well, you know --

DR. SALIVE: So could we not do A then? I think -- I mean we're fine with not doing A.

DR. SCHEUNER: Am I beating you down? I'm sorry.

DR. SALIVE: No, no, no. I think that

you've pointed out valid problems, I question. We're not going to make you vote on one that has the wrong

-- it needs more nuance. It needs to be split. We can't split it at this time.

DR. SPERTUS: So we're voting on how confident we are. If there was a test strongly associated with survival, a screening test strongly associated with survival, what is the confidence? The confidence that we believe that data exists already or the confidence that if there was such a test, we would use it a lot in our practice? So if there's a genetic screening test that's strongly associated with mortality, and there's something I can do about that mortality, then would I use it?

DR. SALIVE: If you're confident that that type of evidence demonstrates effectiveness. That's the question. Does that type of evidence demonstrate effectiveness of a screening program?

DR. SATYA-MURTI: I also interpreted that as would I then be using (unintelligible) recommend that. Survival has shown -- survival benefit has shown --

DR. SALIVE: Well, we're asking about effectiveness of a screening program. So, you know,

that may be one of your ways of weighing this.

DR. SPERTUS: Wait. So this is a test with perfect accuracy. Right? There's no false-positives, no false-negatives. And that's what we're debating here, because he's talking about harm. And I'm thinking like there's no harm. It's a perfect test. So what exactly is the test?

DR. SALIVE: No. We're saying that a rigorous study was done with evidence on survival that's favorable.

DR. TEUTSCH: But you don't know about harms, necessarily.

DR. GUTMAN: And you don't know about quality of life. All you know is that they live longer. Some people live longer.

DR. SALIVE: Well, on average they live longer.

DR. HOLTZMAN: You've gotten -- I guess you're willing to get rid of A. I suggest you also

get rid of B. I mean, you say effective for the

prevention. Now, it's effective for the prevention,

that means it's having an effect on survival. So why bother voting on survival?

DR. SALIVE: What? Are you afraid to vote on that?

DR. HOLTZMAN: I'm not afraid to vote, but you're assumption assumes better survival.

DR. SATYA-MURTI: Well, there is number three. You can -- you can vote number three on those.

DR. HOLTZMAN: Well, we'll get to number three in a minute.

DR. PERFETTO: He'll knock that one out, too.

DR. SATYA-MURTI: Well, question four B is on the table now.

DR. MANSFIELD: Can I say how I interpreted this, which is maybe a little bit different than I've heard, is that if there's good evidence that the genetic screening test can be used, but requires additional diagnostic procedure, should Medicare pay

for it? If there's good evidence that the genetic

screening extends survival, should Medicare pay for

it? If there's good evidence that the genetic screening affects other patient blah, blah, blah, should Medicare pay for it?

Is that what you're asking?

DR. SATYA-MURTI: That's how I interpreted that.

DR. SALIVE: No. We're not asking that. We don't ever ask that question. It may be evidence we use for that decision.

DR. SATYA-MURTI: All right. Let's vote on four B. Be that as it may, with all the confusion in mind, we'll get some metrics down here. If you're not sure, question is unclear -- I don't get to vote, but if the question is unclear, I will take number three.

DR. SPERTUS: Can you read the question to us?

DR. SATYA-MURTI: That's not meant to be -- that's not meant to influence anyone.

DR. SPERTUS: So can you read the question

to us? I mean just read the exact frame of your question you want us to answer?

DR. SATYA-MURTI: I didn't hear that.

DR. SPERTUS: Can you read the exact framing in question that you want us to answer? We've heard half a dozen interpretations. Just read to us exactly what you want us to address.

DR. SATYA-MURTI: For each type of outcome, how confident are you that methodologically rigorous evidence on the outcome is sufficient to infer whether or not screening genetic test is effective for the prevention or early detection of illness or disability?

The voting point here is B, survival.

(Whereupon, the panel indicates their individual vote.)

DR. SCHEUNER: And we're lumping all screening genetic tests together, and we're averaging this out?

UNKNOWN SPEAKER: So the question is, can we reliably tell whether people are alive or dead.

UNKNOWN SPEAKER: Yes, but not for this --

DR. SATYA-MURTI: They live longer.

UNKNOWN SPEAKER: They live longer, but you don't know what the quality of that life is.

UNKNOWN SPEAKER: Any test?

UNKNOWN SPEAKER: This is any test. Right? Any future tests for any disease.

UNKNOWN SPEAKER: Or any tests that we've talked about today.

UNKNOWN SPEAKER: There's no test that exists now that I would rate a four for.

UNKNOWN SPEAKER: What about HMPCC?

UNKNOWN SPEAKER: I would not rate a four for that.

MS. ELLIS: I'm finished. Please make sure you record your scores on your papers also.

UNKNOWN SPEAKER: This is not for tests available today. Right? This is all hypothetical. Can I just clarify that? Thank you.

DR. SATYA-MURTI: It exists out there.

UNKNOWN SPEAKER: What?

DR. SATYA-MURTI: It exists somewhere out there, but we haven't found it yet.

DR. SATYA-MURTI: And C, if you're ready? Other patient-focused health outcomes, for example, functional status and incidence of adverse events. We're voting on C now.

(Whereupon, the panel indicates their individual vote.)

MS. ELLIS: Thank you.

DR. SATYA-MURTI: All right. Record the paper scores. I'm afraid of going to five, but it may be easier, actually. One of the desirable measures of the cost-effectiveness of screening genetic tests for the prevention or early detection of illness or disability. Consider ranking one through three, one being the lowest, three being the highest, for each of the following questions or identify other measures that would be appropriate. A, quality adjusted life years gained due to screening.

(Whereupon, the panel indicates their individual votes.)

UNKNOWN SPEAKER: Hold on. Can they all be threes or all be ones, or we have to rank them?

UNKNOWN SPEAKER: They're not being ranked. It's the same as the last question. We're going to go through all of them.

UNKNOWN SPEAKER: They're all separate?

UNKNOWN SPEAKER: Yes.

UNKNOWN SPEAKER: So we're doing A. Is that correct?

DR. SATYA-MURTI: Yes.

UNKNOWN SPEAKER: We need all of them to get to the quality.

UNKNOWN SPEAKER: We're talking about in the Medicare population. Is that correct? We're limited to the Medicare, over 65 and over?

UNKNOWN SPEAKER: We want the incremental cost-effectiveness ratio.

UNKNOWN SPEAKER: So it's essentially our qualities good outcome measure for --

DR. SATYA-MURTI: Yes. Could quality be used for cost-effectiveness?

MS. ELLIS: Could you please hold up your numbers?

UNKNOWN SPEAKER: So this is five A?

DR. SATYA-MURTI: Yes.

MS. ELLIS: Thank you.

UNKNOWN SPEAKER: Can I change my vote? I'm sorry.

MS. ELLIS: Who's changing their vote?

DR. SATYA-MURTI: B, decreases in incidences of illness or disability or net gains in other patient health care outcomes. How do you -- you want to use this and rank it for question five, cost-effectiveness?

(Whereupon, the panel indicates their individual vote.)

MS. ELLIS: Thank you.

DR. SATYA-MURTI: And C, net changes in lifetime costs of illness or disability. Would that be a measure for question five A, cost-effectiveness?

UNKNOWN SPEAKER: So you're just looking at costs of care as the outcome?

DR. SATYA-MURTI: Yes.

UNKNOWN SPEAKER: And I would assume that if

you were -- the costs were very high -- so you're looking at just the total amount of costs.

UNKNOWN SPEAKER: Right. So somebody -- so you have a test that leads to instantaneous death. Then nobody costs -- anything going forward, there's no -- I mean, that independent of, you know, length of survival or quality of life is a really hard thing, I think, to -- I mean -- at least that's how I'm interpreting it. Am I interpreting it wrong?

UNKNOWN SPEAKER: No.

UNKNOWN SPEAKER: Is this net savings?

UNKNOWN SPEAKER: Yes, but looking at just changes in cost --

UNKNOWN SPEAKER: Change of cost -- outcome -- so --

DR. SATYA-MURTI: Well, without the test, how much would that have cost for the person over, say a ten year -- and with the test, is that going to save, for instance -- is colectomy going to save

additional chemo expenses, visits, and colostomy care?

UNKNOWN SPEAKER: What if it incurs --

UNKNOWN SPEAKERS: (Inaudible.)

UNKNOWN SPEAKER: But that's not a measure of cost-effectiveness, what he just described.

UNKNOWN SPEAKER: But that's not the question. That's part of the analytical approach to determining the overall costs and illness and disability. So all of these factors that you're saying, whether the test is more sensitive or specific or will it measure any of these things, that's all considered in these metrics.

UNKNOWN SPEAKER: But is this question saying that the measure of cost-effectiveness would only be the net changes in cost, or are those changes in relationship to a relevant outcome? If it's only the cost, then it's not a cost-effectiveness measure. If it's that cost in relationship to some relevant outcome, then it's a cost-effectiveness --

UNKNOWN SPEAKER: Yes --

UNKNOWN SPEAKER: Exactly. But at least

they were outcomes.

UNKNOWN SPEAKER: I think you're reading too

much into it. It really is -- in this case, I think it's another technique to capture the overall benefit or harm, and it will be incorporated within that construct. That's my --

UNKNOWN SPEAKER: Because that was A and B that -- we already did A and B. This is just cost. Net cost. You can't have it stand alone is the issue. C cannot be just one specific measure that you determine whether or not you're going to pay for this test or cover this screening test.

UNKNOWN SPEAKER: That cost alone --

UNKNOWN SPEAKER: Cost alone, yes.

UNKNOWN SPEAKER: -- would determine whether or not it's offered or done.

UNKNOWN SPEAKER: If you want to interpret the question like that.

UNKNOWN SPEAKER: It's the same thing of A and B. A and B are just one aspect of something that goes into a cost-effectiveness analysis.

UNKNOWN SPEAKER: That's right. I mean, it's all part of it.

UNKNOWN SPEAKER: All three, A, B and C have to be incorporated into --

UNKNOWN SPEAKER: (Inaudible.)

UNKNOWN SPEAKER: Right, but that's calculated. But it's calculated in --

UNKNOWN SPEAKERS: (Inaudible.)

UNKNOWN SPEAKER: Yes. I think you'll be able to -- I think you'll be able to calculate that.

DR. SATYA-MURTI: Are we ready to give a number for Maria?

UNKNOWN SPEAKER: I don't interpret it that way. I don't interpret the question that way.

(Whereupon, the panel indicates their individual vote.)

MS. ELLIS: Dr. Richner, are you voting?

DR. RICHNER: I'm going to vote. (Indicating.)

MS. ELLIS: Thank you. Please don't forget to record your scores on your papers, and I'll come by

and pick them up now.

DR. SATYA-MURTI: We're down to two or three

discussion items. Question six, what are the desirable methodologic characteristics of studies of cost-effectiveness for screening genetic tests for the prevention or early detection of illness or disability? I think we have answered some of that on five, but in view of the need for discussion, may we have some discussion?

UNKNOWN SPEAKER: Why are these so special?

UNKNOWN SPEAKERS: (Inaudible.)

DR. SATYA-MURTI: Does anyone have any particular yen to naming some items for six?

DR. GRANT: I think it's been alluded to before for the purposes of -- if it's done in the context of a model, obviously one has to have age-correct parameter estimates and the accompanying degree of uncertainty with them. I think it's been pointed out here many times, that a lot of the evidence related to these tests has not been obtained in this relevant population and, accordingly, I think

that needs to be reflected in any modeling or cost-effective exercise.

You know, there are lots of methodological standards for cost-effectiveness studies and doesn't really apply here.

DR. SATYA-MURTI: You say cost-effectiveness is a process that comes necessarily after determining clinical validity and usefulness.

UNKNOWN SPEAKER: Of course. It has no value. It can't be cost-effective --

DR. SATYA-MURTI: (Inaudible) proximal to that, where we haven't decided. Many of them -- all right.

Question seven discussion?

DR. MANSFIELD: Can we still talk about six? I was going to say, I don't know if it's a methodological characteristic, but given that health care costs vary across the country, we'd need to have very good geographical representation to be accurate.

DR. HOLTZMAN: I think that's a great point. I think the things that were mentioned in the previous

question are important. But I'd emphasize the word

net in five B. I mean, we need to look at adverse

events or harm that results from screening in developing cost-effective --

DR. PERFETTO: I would also add that there are standards out there for cost-effectiveness studies. And that methodologically, these studies should meet those standards.

DR. TEUTSCH: I think a critical issue for Medicare is particularly the perspective. I think the recommendations from the panel on cost-effectiveness in health and medicine are probably the ones that we generally should be following. But they recommend taking a societal perspective, and I think that should be done. But one can make the case that for a payer, you should probably also look at payer's perspective, which is fine. But I do think it would also have to be done in the context of a societal perspective.

MS. DAVENPORT-ENNIS: And I think from the societal perspective, we feel that if you're looking at cost-effectiveness, you really want to ask two

fundamental questions; do they accelerate the time of

the diagnosis and also assist in leading to the use of

correct therapeutic interventions, which is certainly one of the hopes that would imbue cost-effectiveness.

DR. SATYA-MURTI: Well, talking about accelerating diagnosis, it might fit in with question three as well. Are there ethical issues particular to screening genetic testing that may alter the methodological rigor of studies of genetic testing?

When you say accelerate in a beneficial way or just produce insomnia years ahead?

MS. DAVENPORT-ENNIS: Hopefully in a very positive way so that the patient is going to get the answers quicker. And when the patient gets the answer quicker, there will be less cost impact to the system. And when they get those answers, they are correct answers.

DR. SATYA-MURTI: Yes. That is one ethical issue.

DR. HAYES: There are people on this panel who know a lot more about it than I do. But there are

enormous guidelines and governing bodies that have

spent lots of time about the ethics of germline

genetic testing as opposed to somatic changes. And again, this question to me was sort of, do you ride the bus or take your lunch to school.

There are enormous ethical issues to germline genetic testing that don't pertain to somatic testing. So, for example, doing mammograms is unlikely to lead you to be discriminated against in your job and that sort of thing, whereas, having a BRCA1 is likely to. I don't think that alters the methodologic rigor of the studies and all the end points and things we just talked about.

But it certainly alters the kinds of issues about confidentiality and downstream effects on family members and that sort of thing that are affected. So again, I'll say this question has important components within it. But it doesn't ask the question I'd have asked, you know, which is that there are two separate issues here.

Is the methodologic rigor of genetic testing

important? And the answer is yes, just like it would be for any medical intervention. And are there

ethical issues unique to genetic testing? And the answer to that, I think, is yes, relative to other kinds of screening and testing.

DR. DANIS: I would sort of echo what was just said. I think methodologic rigor is important in these tests. And it's important that accuracy be as important, if not more. As we said before, if you're likely to be doing these tests once -- so I don't think any ethical concerns reduce the obligation regarding rigor, methodologic rigor.

DR. MANSFIELD: So I don't think this is unique to genetic tests, but testing in which the sample required in order to perform the testing is actually invasive or harmful in itself may alter the way that you run your study and who you enroll and so on. If it's a brain tumor that you -- you know, you'd have to do a brain biopsy of, you may want to do fewer of those if it were likely to have the side effect of making someone paralyzed or something like that.

DR. SATYA-MURTI: I was thinking some of us would be talking about false positives and the ethical

consequences of that, or is that implied in what you have said?

DR. WEINER: I don't know quite where to place it, except here one day, there won't be any gene testing. All of our genes will be online. You know, it will be gene-chipped, and it will be in the EMR. And the health system will, retrospectively, go back. And once we learn more about the genes, we'll be able to analyze it. And hopefully, we all have access for research, but God help us for, you know, individual implications. And I may be off by a little, but not by much, I don't think.

And what that means for us today, I don't know. But over time, it's going to happen, I think. And they've been trying to do that in Iceland, but they ran out of money so --

DR. HOLTZMAN: Well, there are two questions. It's very hard to know whether this really fits under methodologic rigor. Two points; one is if

you're using archived specimens with identifiers, a

consideration has to be given for what you're going to

do in terms of notification or whether you should even use those specimens without a (inaudible) and informed consent.

DR. WEINER: That relates to what I said. Yes.

DR. HOLTZMAN: The second is, when you are developing genetic tests, you have to be prepared to know what you're going to do if you have a positive result of an identified proband, let's say, in terms of informing relatives, particularly if you're dealing with Mendelian disease. So those have to be considered in the planning of the study.

DR. SATYA-MURTI: Were all the methodological requirements higher than for what you said and also for the false positive and the fear factor as well as commercialization? So, therefore, unlike, say, doing a body scan, body CT or spinal CT, this would be even more vital, to make sure that the methodology is even more sound than doing an MRI scan

and showing that you have a bulging disc. So I thought the bar would be higher for this.

DR. HENDERSON: I do think another potential compromise of the methodologic rigor is, the fact that you're going through the proband in each case. And they do have some control over whether there's access or no access to the relatives. So that adds an additional dimension and potential bias that has to be taken into consideration.

DR. SATYA-MURTI: If they're willing to discuss their results with the relatives?

DR. HENDERSON: Right. In other words, you can't -- let's say you're seeing a patient that you now want to study, and you demonstrate, for example, that they have genetic markers. You say, I want to study the various relatives. You can't really approach any of those people without the patient's permission. It's fundamental to the ethics of medicine.

DR. SATYA-MURTI: This is true.

DR. HENDERSON: And, therefore, the patient

becomes a gatekeeper, if you will, to access that --

the patient may decide that they're only going to

provide information or access to some of their relatives and not to others or to no relatives. So that becomes -- we do have that in other studies as well. For example, physicians are gatekeepers and introduce biases regularly into studies. But now they will still be there and still introducing those biases. We now have the biases of the patients. (Inaudible.)

DR. PUKLIN: I think that the HIPPA guidelines don't apply to diseases of this sort when there are other family members that are involved, and the information can be transmitted freely between family members by the physician without the consent of other family members.

DR. HENDERSON: So you think obviously if Mrs. Jones and I decide that I want to contact his daughter and do a study, I can just pick up the phone and call her daughter and say, we'd like to have you come in and do a genetic study without having told

Mrs. Jones in advance I'm going to do that?

DR. PUKLIN: If there's reason to believe

that the disease is widespread in the family, you don't have to go through all the paperwork to get permission from everyone to contact everyone.

DR. HENDERSON: I don't think this is a HIPPA issue. I think there's a fundamental ethical issue of medicine.

DR. SCHEUNER: (Inaudible) picking up the phone and --

DR. HENDERSON: No. You need -- the patient should consent, but you don't have to go through paperwork, documentation. You can divulge the information among the family members who are involved. I agree. That wasn't the issue. No. No. I agree. That wasn't the issue.

The issue was, you still would have to have the patient's permission to call her daughter or call her mother or other people. You wouldn't start calling those people in to do studies without the permission of that patient. That patient becomes an

important gatekeeper.

And then I'm saying further you'd have to

have one for each one. You wouldn't -- she -- you wouldn't say, well, I can't call your relatives, and then you choose, for example, to call them. You would go through -- I think any physician that I know, would make certain that they had the permission independent of any legal HIPPA constraints or any paperwork. Leaving all those things aside, that's the way medicine is practiced.

DR. SCHEUNER: So this is this duty, to warn issue, an ethical issue for physicians. And there are two legal precedents, I guess. One was with medullary thyroid cancer in the state of New Jersey, I believe, where the court said that it was the physician's duty actually to inform an at-risk relative, as if it was an STD or something. That there was a public health issue, and that their duty was to inform that at-risk relative.

Whereas, there was another case -- I think it was Florida -- or I'm getting the dates mixed up --

where it was familial adenomatous polyposis. And it was sufficient for the physician to inform the

patient, that this genetic information had implications for other family members and to leave it at that. It was something -- I'm probably getting the cases mixed up.

But it's a question of, is it sufficient to just tell the patient in front of you that we've identified this genetic result, and it has implications for other family members? Is that sufficient in terms of duty to warn? Or are you obliged to actually go and seek out those at-risk family members?

DR. PUKLIN: Let me ask you another thing. So there were a number of genetic studies that have been done already, where in the consent form the patient was told, you know, we would like to have you donate genetic material. There are no current genetic tests for cardiovascular disease. We are going to, in the future, use your blood for that genetic test, but we promise you we will never contact you to discuss

the results or do anything.

And then you discover a mutation that's very

adverse for the patient. I mean, I think it's a huge ethical issue. I don't know what the answer to that is. But, you know, it's a real challenge because you've promised the patient in the consent form you're not going to call them. And it was on that promise that they donated their genetic material to advance science and to help figure out other causes and associations. And then, you know, knowledge is advanced, you discover something, and what do you do now?

DR. HENDERSON: Well, I'm the chairman of the IRB at my university. You can construct these consent forms any way you want. And so if you think that you're doing the patient a favor, you can tell him you're going to -- you'd like to store their blood, have it put in a repository for known testing. And then you can tell them that you will notify them of the results of the blood tests when they come back, if they would like to have it.

Or you may construct it and ask them to give

you permission to draw the blood for some known tests

that are going to be done on it and ask them if they would be comfortable without being notified for it. So you can construct this any way you like.

And the new issue that's come up is to bank the tissue in either a university repository or a commercial repository for research at a later time, looking for markers that are yet undetermined in all these diseases. And in those cases, the patients are separated completely from all the identifying features that would identify them, and the specimen is in a repository only with the patient's history, but no identifiable characteristics. So there's no way the patient would be identifiable. Only their medical history would be. You have the prerogative to set the study up the way you want.

DR. SATYA-MURTI: I have to intervene and give the unpleasant news that we have a shuttle leaving at 4:00 to the airport. I apologize for truncating this. Is that correct?

MS. ELLIS: Yes. For the panel members who were picked up at the Westin, the shuttle that picked

you up will be taking you back to BWI airport, and it's been sitting outside. So it's only given us until 4:00 o'clock. Four o'clock, he'll be pulling off. And then I have to try to find cabs.

DR. SATYA-MURTI: So that raises the issue, question eight. Does the age of Medicare beneficiary population present particular challenges that may compromise the generation and/or interpretation of evidence regarding genetic testing?

DR. SPERTUS: Yes, a lot. They were brought up really well. It's the incremental difference in a population that survived for 65 years or longer. And even more so at 80 years and 85 years. And so there's a lot of unique issues about the Medicare population. There's a real paucity of data. And so those are really going to be very important considerations, in trying to weigh what might be a reasonable test to cover for, you know, all populations specifically in Medicare because they, you know, have a survival

advantage.

So even if they have a mutation, they may

have a much better prognosis with that mutation because of other factors than other patients in whom that mutation was associated with the adverse events.

MS. RICHNER: But conversely, we also have a lack of information in the Medicare population that was expressed earlier on, too, that we have very few studies that are actually done in the over-65 population. And I think that's an important point here, that we want to make sure that we embrace the idea of looking at all populations and then make inference to the Medicare population.

When there's lack of evidence or lack of information in the over-65, I think it's really critical, especially given health reform and universal coverage is on the table. And it's very likely that we're going to be covering all the uninsured in the U.S., and Medicare's going to be doing it.

So, I mean, I think we need to look to the future and really think about, you know, expanding how

we examine data beyond just 65 and over for this particular topic.

DR. HENDERSON: So I just want to consolidate. The last two points made was one that you'd been making earlier in the day. So essentially, you have to consider the fact that, for this older population, there may be a difference in the biology of the disease. Secondly, we know there's a difference in the biology of the host, which is a point that you made several times today. And thirdly, we know that we have very little data. So somehow or another you're going to have to figure out how to get more data, in order to address both these issues, the biology of the host and biology of the disease.

MS. DAVENPORT-ENNIS: And I would like to add two additional points. Not only those three points, but also we also know that there's a likelihood of co-morbid conditions --

DR. SATYA-MURTI: And polypharmacy.

MS. DAVENPORT-ENNIS: And polypharmacy that will impact the result of what we get.

DR. HAYES: And co-mortal. The patient has less time to benefit (inaudible). Most screening

techniques take eight to -- cancer, at least, eight to ten years to see a survival benefit. An 85 year old probably isn't going to have much chance to benefit