Secretary's Advisory Committee

on Genetics, Health, and Society

Twenty-second Meeting

June 15-16, 2010

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Secretary's Advisory Committee on Genetics, Health, and Society

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M O R N I N G S E S S I O N

(8:33 a.m.)

Opening Remarks

by Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Good morning and welcome to the twenty-second meeting of the Secretary's Advisory Committee on Genetics, Health and Society. I think everybody is grateful this time that we are not battling the blizzards. I think most everybody, with the exception I know of Charmaine and maybe one or two others, managed to escape the great blizzard of 2010. We are in better shape today with just a little rain.

I wanted to thank actually, going back to that, everyone who was very accommodating in adjusting the schedule back in February and also to Allison who I know bailed many of us out by changing our tickets and allowing us to get out before the great storm.

But on to today's meeting, as usual the public was made aware of this meeting through notices in the Federal Register as well as announcements on the SACGHS website and listserv. I want to welcome the members of the public in attendance as well as viewers who are tuning in via webcast. As always, thanks for your interest in our work. We will have public comment sessions this morning at 11:15 and again tomorrow at 10:15 for any of you who wish to make public

comments and have not already signed up; please do so, so we can anticipate your presentations.

Well we have several topics to cover for this meeting. We will begin today with updates on some federal activities. We will first hear from NIH's Chief of Staff, Kathy Hudson, who will provide an overview of the Genetic Testing Registry and a new partnership between NIH and FDA on translational research.

She will be followed by an update on the Interim Final Rule for initial standards, implementation specifications, and certification criteria for electronic health records by Dr. David Hunt from the Office of the National Coordinator for Health Information Technology.

Then we will hear from Bin Chen from CDC on recommendations for good laboratory practices for biochemical genetic testing which were developed by CLIAC, the Clinical Laboratory Improvement Advisory Committee.

After lunch we will be spending the rest of the afternoon discussing the implications of affordable whole-genome sequencing led by our committee members, Charis Eng and Paul Billings.

Tomorrow's agenda will include a session on genomic data sharing followed by a session on issues and concerns related to carrier screening.

Our final agenda item will be to discuss a briefing

paper prepared by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children on the retention and use of residual dried blood spot specimens.

However, before we move on to the first topic I have a few updates. Since our last meeting, we have finalized our report on Direct-to-Consumer Testing and our report on Gene Patents which you received from Sarah by email a few weeks ago. We also released our draft report on Genetics, Education and Training for public comment.

The committee's report on DTC Genetic Testing was transmitted to the Secretary in May and it is available on the SACGHS website. For members of the public attending our meeting, there is a handout with the URL for the report. I would like to thank Sylvia Au for her leadership in guiding this report and members of her task force for their work. Sylvia has rotated off the committee so no more chocolate covered macadamia nuts unless Adam brought some.

(Laughter)

DR. TEUTSCH: No pressure Adam. But we hope she listens to our webcast and we appreciate all the work she did for the committee over several years.

The Gene Patents Report has also been transmitted to the Secretary and can be found on the SACGHS website. A handout with the URL is also available for attendees.

In March Jim Evans and Rochelle Dreyfuss briefed NIH

Director Francis Collins on the report's findings, conclusions, and recommendations. Dr. Collins was particularly interested in the question of whether whole-genome sequencing will infringe gene and method patents. As a result, after the meeting, Jim and Rochelle sent Dr. Collins a letter that provided additional analysis and examples of patents that may be infringed by whole-genome sequencing. The issue of gene patents and whole-genome sequencing is also discussed in an April 15, 2010 *Nature* editorial that comments on the report and you will find a copy of that editorial in your table folders.

So now that our report is being weighed by the public and Secretary, I want to again thank Jim Evans for his dedication and leadership in bringing this report to closure. I also want to thank Rochelle Dreyfuss, Paul Billings, Sheila Walcoff, Paul Wise, and Mara Aspinall all of whom labored hard after our October 2009 meeting as the report was revised.

I would be remiss if I did not thank our staff, particularly Darren Greninger in this case, for their dedication to advancing our work; it was an enormous amount of effort.

We are going to continue to monitor developments in the area of gene patents and genetic tests as we move on with our other priorities. Among those priorities are improving genetic education and training. In February Barbara provided

us with an extensive review of the findings and recommendations on the Genetics, Education and Training Task Force and the committee approved the draft report and recommendations for public consultation.

During the past few months, the draft report was revised and shortened to improve its readability but the recommendations remain as we approved them. The draft report is now out for public comment until the end of the month and you should have all received Sarah's email announcement of the report's release for public comment; we welcome your personal comments as well as those of your colleagues. I want to give a special thanks to Barbara for her continuing leadership on this project.

In February we also approved a commentary for submission to a medical journal and it has been submitted to *The New England Journal of Medicine* last month and we are waiting for more information about its status. A copy of the commentary is in your table folders as well.

In addition to the presentation and its recommendations for good laboratory practices, CLIAC has also been working toward the development of a notice for proposed rule-making to update requirements for proficiency testing. This action is consistent with the recommendations in the SACGHS report on the Oversight of Genetic Testing. During the process of developing the proposed rule, a CLIAC working group

is engaging with constituents who would be affected by a change in PT requirements and the proposed rule is expected next year.

I would also like to provide an update on GINA. The draft final regulation implementing Title II of GINA was cleared by the Office of Management and Budget in early April. The EEOC is now engaged in its internal review process. Once the commission has voted to approve the regulation, it will be published in the Federal Register.

According to the EEOC, there have been approximately 80 charges filed on Title II of GINA since it became effective on November 21, 2009. The charges which came from across the country concern issues such as improper requests for family medical history during employment-related medical examinations, improper disclosure of genetic information, termination of employment, and denial of health benefits based on genetic information. An article about one such discrimination complaint is in our briefing books at Tab 10.

Another genetics-related bill may also be on the horizon. Representatives Kennedy and Eshoo recently introduced The Genomics and Personalized Medicine Act of 2010 which has a number of provisions designed to advance genomics research and personalized medicine. Among other things, the legislation would establish an Office of Personalized Healthcare in the department and a national biobank and

include measures to improve the education of health professionals in genomics. Copies of the bill have been included in your folders in case you would like to review other provisions of the legislation.

I also want to mention some changes in our committee roster. We would like to thank Dr. Barry Straube for his service as the Centers for Medicare and Medicaid Services *ex officio*. And welcome Jeff Roche who has, of course, been with us on many occasions and Jim Rollins as the new CMS *ex officios*.

We also want to thank Robinsue Frohboese for her service and dedication to SACGHS as OCR's *ex officio*. Robinsue has moved to a new position in the Department of Justice and Jennifer Weisman is taking her place. So welcome back; you have been here before. It is good to have you official.

The official *ex officio* from EEOC has also changed with the appointment of a new Commission Chair, Jacqueline Berrien; so welcome to her as well.

(Lunch/Dinner logistic discussion)

DR. TEUTSCH: So before we get into the substantive part of our meeting, Sarah you are on to tell us about ethics.

MS. CARR: Yes, to remind you all; thank you Steve. As you all know, you have been appointed to this committee as a special government employee. Although you are in a special

category, you are nonetheless subject to the rules of conduct that apply to regular government employees. The rules are outlined in a document called Standards of Ethical Conduct for Employees of the Executive Branch which you each received when you were appointed to the committee and I am going to highlight two of those rules as I usually do.

One is about conflicts of interest. Before every meeting you provide us with information about your personal, professional and financial interests, information that we use to determine whether you have any real, potential, or apparent conflicts of interest that could compromise your ability to be objective in giving advice during committee meetings. While we wave conflicts of interest for general matters because we believe your ability to be objective will not be affected by your interests in such matters, we also rely to a great degree on you to be attentive during our meetings to the possibility that an issue will arise that could effect or appear to effect your interests in a specific way. We have provided each of you with a list of your financial interests and covered relationships that would pose a conflict for you if they became a focal point of our discussions. And if this would happen, we ask you to leave the room.

Also we are close to the Capital today so I want to remind you about lobbying. Government employees are prohibited from lobbying and thus we may not lobby, not as

individuals or as a committee. If you lobby in your professional capacity or as a private citizen, it is important that you keep that activity separate from the activities associated with this committee. Just keep in mind that we are advisory to the Secretary of Health and Human Services; we don't advise the Congress.

And as always, I thank you for being so attentive to the rules of conduct.

DR. TEUTSCH: Thank you Sarah. So all right, let's start off by hearing from our very special guest this morning, Dr. Kathy Hudson, who many of you know as Chief of Staff at the National Institutes of Health.

Kathy has worked with this committee on a number of important issues over the years and was really an instrumental part of our Task Force on the Oversight of Genetic Testing and it is great to have her in such an important position within NIH.

She is going to tell us about the Genetic Testing Registry which addresses one of the committee's recommendations in the Oversight Report and give us an overview of the partnership between NIH and the Food and Drug Administration to advance translational research and medical product development.

Then we will open up the floor for discussion and questions from committee members. A copy of the Request for

Information to provide input to NIH as it plans the development of the Genetic Testing Registry is in your table folders. So Kathy it is really a pleasure to welcome you back and we look forward to what you have to say.

Overview of the Genetic Testing Registry and A New Partnership with FDA on Translational Research

by Kathy Hudson, Ph.D.

DR. HUDSON: Thank you. It is a pleasure to be here and thank you very much for inviting me. It is a little bit like coming home. I realize I have appeared before this committee, frequently impatient and banging on the podium and I will not do that today.

(Laughter)

DR. HUDSON: I am going to talk a little bit today about the Genetic Testing Registry and sort of what we have in mind and what we would like to seek from you. But I thought that I would talk a little bit more broadly about issues affecting personalized medicine before launching into that.

It was probably close to a year ago when Francis Collins called me up and indicated that the President had tapped his shoulder and asked him to be the new Director of the NIH and he said that he would like me to come back to the NIH and be his Chief of Staff and I told him “no freakin' way.”

(Laughter)

DR. HUDSON: I clearly lost that argument; he can be pretty persuasive. So I spend a lot of time in this building, Building 1 at the National Institutes of Health. I don't get out that much so it is a pleasure to come down here today.

(Slide)

Before Francis came to the NIH he spent some time thinking about the horizon in biomedical research and what opportunities were out there. And I am sure that you have seen and heard talk about his five opportunities for the NIH and these are really guiding the work that we are doing to put together our budgets for future years.

(Slide)

So those themes include applying high-throughput technologies to understand fundamental biology, translating basic science discoveries into clinical applications and I will talk a little bit more about that, putting science to work for healthcare reform and already we have funded quite a few initiatives in this arena and we will be funding more, encouraging a greater focus on global health, and reinvigorating and empowering the biomedical research community.

(Slide)

So these are sort of the principles that are guiding us and, of course, we are at a very unique time in biomedical research because not only is Francis an inspiring and

ambitious leader but we also have a very pro-science administration with the President and Kathleen Sebelius and all that they have brought with them into the Administration.

We were fortunate enough to have the President come visit the NIH in September. I started on September 3 and was told that my first duty was to get the President to come to NIH; I was successful in that endeavor. And this was a quote from his appearance at NIH in which he talks about his commitment to science.

Not only is he committed to science but as we all know, he is committed to health and healthcare reform and really made healthcare reform a reality in a remarkable period of time. For those of us living through it, it seemed like it was taking forever but it was only about fifteen months from the time that he originally proposed healthcare reform in March of 2009 until it was enacted.

(Slide)

This is a cartoon that I had when I was at Johns Hopkins on the Coffee Board and some people in the room will remember it being in the coffee room. I think this really does reflect sort of the new spirit that the scientific community has. There was tension and some animosity between NIH and the Administration in the last eight years and now it feels like everybody is dressed up in the same uniforms and playing for the same team so that is very refreshing and it

makes it much easier to get things done.

(Slide)

I want to say just a word about healthcare reform and particularly what healthcare reform means for us at NIH and for the biomedical research enterprise. I am not going to talk about the Comparative Effectiveness Research provisions in healthcare reform but do want to say a few words about the Cures Acceleration Network which was included in healthcare reform.

(Slide)

What the Cures Acceleration Network is basically seeking to do is to bridge the valley of death and increase the rapidity with which we can translate basic research findings into medicines in people's medicine cabinets. This was highlighted last month in an article in *The New Yorker* by Malcolm Gladwell and this article in *Newsweek* talking about this fundamental problem of being able to bridge the valley of death.

(Slide)

So the pipeline for drug development is familiar I am sure to many of you. What we do at NIH is really predominantly focused on the left end of this pipeline in disease identification, target identification. And where we have started to spend more resources is in high-throughput screening in order to develop compounds that may end up being

useful in clinical practice, leading to preclinical research and then of course through the FDA process.

We have, over the course of the last year, made new investments in this pathway and will continue to make new investments in this pathway both through the NIH Director's Common Fund where he has about $540 million at his disposal directly to allocate to high priority trans-NIH research initiatives. Among those are the Molecular Libraries Initiative, Therapeutics for Rare and Neglected Diseases project and others.

In order to sort of bridge the valley of death, we are going to have to partner with pharmaceutical companies, with biotech, and with our academic-funded centers including the Clinical Translational Science Centers.

We have, over the last nine months, put together some new and I think exciting partnerships with the Food and Drug Administration because that partnership is going to be critical, not just an interaction between Dr. Collins and Dr. Hamburg, the Commissioner of the Food and Drug Administration, but effective interactions at all levels between our two agencies.

(Slide)

And so in February we announced a new NIH FDA Joint Leadership Council which will be co-chaired by Dr. Hamburg and Dr. Collins. Kathleen Sebelius, the Secretary, came out to

NIH to join us for that announcement. And one of the first things that that joint effort has done is to make available a funding opportunity in regulatory science. We have those applications in, they are about to be reviewed, and together the two agencies made available nearly $7 million for that.

(Slide)

A week or so ago, a couple weeks ago, we had a public meeting where Jesse Goodman, the Scientific Officer from FDA, and I listened to public input on what were the high priority issues that FDA and NIH should tackle as we begin this partnership together. And with Amy Patterson's help and Sarah Carr and their teams, we are planning a meeting for the Joint Leadership Council hopefully in June or July.

(Slide)

So back to the Cures Acceleration Network, what will the Cures Acceleration Network do? We already have efforts ongoing in this translational pipeline. And what the Cures Acceleration Network will do will provide, if it is appropriated, will provide additional funds and specifically will provide us new ways of doing business so that we can be more nimble and flexible in our approach.

(Slide)

So this is the goal from the legislation that was included in healthcare reform: to dramatically advance development of new treatments and cures for debilitating and

life-threatening diseases by reducing barriers between laboratory discoveries and clinical trials.

And the legislation is really focused on high-need cures. Of course if you or your family is affected by a particular disease or disorder, that is by definition a high-need cure, so we will have to spend a lot of time I think focusing on how to define the criteria for what is and what is not a high-need cure.

(Slide)

The Cures Acceleration Network was authorized for $500 million in FY2010, which is this year. That is not an appropriation so we do not have a check. The Network would be situated in the Office of the Director and it would provide some nifty funding and other authorities that would allow us to have more flexibility in how we fund research. Currently, as you are well aware, from the time that we have an idea of something that we want to fund until we can put money into the hands of the people who can do it, it is a fairly long process and this would provide other transactions authority which gives us sort of flexibility that some of you may be aware of in DARPA where you can quickly start a project and if it is not going forward and is not succeeding, you can also kill it quite quickly.

(Slide)

There has been a lot of support for the Cures

Acceleration Network from industry and patients. This was a letter sent to the Senate in April. There has been a similar letter that has been sent to the House by a remarkable group.

(Slide)

You cannot read this but it is to make the point that it is a large number of diverse advocates from across medicine and patient advocacy that are supporting this.

(Slide)

So a good cure, of course, requires a good diagnosis. And in fact the definition of a high-need cure is not just a medicine in the bill, it includes a biological product or a device. And so in fact the development of new diagnostics could be a high-need cure as well.

(Slide)

So I want to talk a little bit about what we have been doing lately with genetic testing and with where we are with the Genetic Testing Registry. So as you all know, genetic testing has changed a lot. It has increased in number.

(Slide)

Genetic testing is increasing in complexity as we read about virtually every day.

(Slide)

Genetic testing has changed in its availability; being offered more frequently, directly to consumers, either

through the internet or in some cases attempts to make it available in retail drug stores.

(Slide)

It is available to you if you want to be an undergraduate at the University of California at Berkeley.

(Slide)

And this is the Pathway Genomics Test which I am sure you are all familiar with.

(Slide)

Genetic testing has also increased in clinical relevance from the olden days when most of the tests were available for high-penetrant Mendelian disorders that would tell you your high probability of developing a devastating disorder where there was no intervention available. So there was this therapeutic gap; you could get the information about your future but do little about it. To today, where increasingly you have refined information about the risk for future disease and increasingly having the ability to do something about that; having some actionable information.

(Slide)

My favorite example these days is Plavix which is, I think, the second most prescribed drug and we know that nearly one-third of the population does not respond to this drug because of variance in the P450 pathway.

(Slide)

Because it is relevant to the discussion today, I want to just review the drug relabeling that went on in the clopidogrel case because I think it is an interesting challenge that we face today as a part of how we deal with the diagnostic side of things and how we are going to deal with the drug relabeling side of things.

So if a drug is already out on the market and we find that there is a subpopulation that responds adversely or with whom it is not efficacious, the FDA and the sponsor and the diagnostic developer have to work in a rather complicated way to get that information into a drug label.

(Slide)

Clopidogrel was initially approved in 1997. It was relabeled in 2009 to add pharmacogenetic information but it did not really say much except that genes are involved in metabolism of this drug and clopidogrel is a prodrug and it has to be activated by the enzyme in order to be effective.

In November of 2009, that precaution was upgraded to a warning. And then in March of this year, just a couple of months ago, there was a black box warning added to the label of Plavix indicating that CYP2C19 testing would indicate whether or not people would respond to the drug or not.

(Slide)

I want to sort of switch gears just for a second and talk about -- I know that you have your report out on

patenting and I know that it has been transmitted to the Secretary and certainly this case from March comes to bear in terms of the development and availability of a diagnostic test.

So I am sure you are familiar with the Sweet decision that was brought by -- the plaintiff in the case was the Association of Molecular Pathology and they challenged the validity of claims of BRCA1 and BRCA2 held by Myriad Genetics.

(Slide)

And if you have not read the case I really recommend it to you; it is fascinating reading. What is interesting to me, and I am not a lawyer, is that in the decision the judge refers not at all to any of the previous cases that have been argued over the patentability, over specific gene patents, but rather argues that DNA is not patentable subject matter period. And so he is clearly not speaking to the Appeals Court, he is speaking to the Supreme Court in writing this decision.

So the two findings, rulings in his case, were first that “isolated DNA” containing sequences found in nature are unpatentable subject matter and secondly that the claims for comparing those patient sequences to wildtype sequences is an abstract mental process and thus the comparisons of DNA sequences are unpatentable subject matter.

So these are two very sweeping rulings by the judge.

To my knowledge, Myriad has not yet appealed the court decision. And also to my knowledge, the Association of Molecular Pathology has not appealed the decision. They could appeal this decision because there were some changes in the final decision in terms of whether or not the PTO was subject to the case.

(Slide)

So I think this case raises some important questions in terms of its implications for the development of DNA diagnostics. I think it also has potentially important implications for therapeutics to the extent that it could be interpreted broadly to apply to nucleic acids used therapeutically.

(Slide)

So I am going to sort of skip through some of this and get to the issue of the Oversight of Genetic Testing which of course I have had a long-standing interest in. I am happy to tell you that today in *The New England Journal of Medicine* Dr. Collins and Dr. Hamburg have published a perspective called The Path to Personalized Medicine which -- look at that, it is 9:00 -- it is now online and copies of it are available over at that table. And it is an interesting piece because it is the shared vision of the NIH Director and the FDA Commissioner on what they feel are the key steps along the pathway to realizing personalized medicine.

(Slide)

Specifically they say that "NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make accurate information about tests readily available." So I think that is a pretty clear statement of a shared vision that these two leaders have and now we will move forward, of course, in implementing that vision in a coordinated way.

(Slide)

Of course this comes at an interesting time. The Congress has been paying quite a bit of attention to genetic testing oversight of late. Congressman Waxman, the Chairman of the Energy and Commerce Committee, and his investigations in oversight subcommittees have been looking deeply into this issue and launched an investigation into genetic testing specifically focused on some of the DTC tests. They sent letters to the manufacturers of those tests asking them for a fairly substantial amount of information. I think they asked for it by June 23, so that should be resulting in some sort of analysis by the committee soon.

Dr. Collins is testifying before this committee, the Health Subcommittee of the Energy and Commerce Committee this

afternoon and I anticipate that questions about genetic testing oversight will come up.

(Slide)

Subsequent to the Energy and Commerce investigation, FDA sent letters, untitled letters, to a number of these companies indicating that they thought that these products may be devices and that they invited these companies to come in and talk with them. It is not the kind of invitation that you ordinarily want to get. And so those letters have gone out and I would expect that those companies are moving rapidly to come meet with FDA because FDA needs to now provide them with indications of what is required, what FDA is asking for.

(Slide)

So we are not a regulatory agency. We have been working with FDA and have lots of friends and colleagues at FDA who we have been interacting with over the past several months and will continue to do that.

On our end, what we are able to do, is to build this Genetic Testing Registry. And so the goals of this Registry, which were inspired by you in your Oversight Report, is to improve research and public health through increasing transparency, increasing access to information, and increasing competition. And in the process of building this Registry we are really seeking broad public input.

(Slide)

So we have published a Request for Information both in the NIH Guide and in the Federal Register. I think it was published in the Federal Register last Friday, is that right Sarah? And so it is available for public comment for 30 days. We posted a series of questions; we may not have posed all the right questions and I will run through some of those in just a minute.

The team of people who have been working with this at NIH have involved both the Office of the Director with Francis Collins at the helm and also the informatics guys at the National Library of Medicine in the National Center for Biotechnology Information; the people who bring you all the myriad databases that you can access that have genetic information in them now and of course bring you PubMed.

So the really exciting thing to me about building this Registry is that it is going to be integrated into these other electronic resources within the Library so that you can easily in a semi-automated way go from one resource to another resource to another resource.

So we are seeking input. We hope to gather information from you all over the course of the next 30 days and then have some public meetings and private meetings as well. So if you have information that you would like to share with us, our doors are open and we would be happy to sit down and meet with you.

(Slide)

These are some of the issues that we are seeking comment on and for some reason the word “test” is bigger than the other ones. So I will not read through these because you are all literate.

(Slide)

And these are our additional questions that are posed in the Federal Register notice. And I think I will stop there and say that I am really excited to be able to implement one of the Secretary’s Advisory Committee on Genetics, Health and Society recommendations and we are hoping that we can get your input and develop a beta database for some testing and get the thing up and running in the next calendar year.

We have big challenges ahead in all areas of genetic medicine and building this database will help us get there. So I will end with that and be happy to take your questions.

Question and Answer Session

DR. TEUTSCH: Great. So let’s start with Andrea and then Paul.

DR. FERREIRA-GONZALEZ: Kathy thank you very much for a wonderful presentation. It is good to see that one of the recommendations is actually going to be moving forward and you actually were a part of that too.

And I understand that this is still an evolving process so I just wanted to find out if you have in mind to

have a single Registry for all-comers or are you twirling with the idea of having one for healthcare providers and another one for consumers, as the information might have to be related in a different way to be understandable for very different groups.

DR. HUDSON: We would certainly be open to comment on that very topic. I think that, at least in my own head, I had been imaging a single database that would be searchable by all sorts of terms and would have information that would be fairly technical because of the nature of the information that we are trying to contain. Whether it could then link over to other more lay resource is certainly a possibility but I had not envisioned there being two disparate sets of information for providers and researchers and patients.

DR. FERREIRA-GONZALEZ: And a follow-up question to that one, are you envisioning mechanisms to assure the accuracy of the information that will be put in the Registry?

DR. HUDSON: So that is a great question. We will not be double-checking the information that is submitted by a laboratory or a manufacturer, so we cannot really annotate it.

I think that probably the best example of a database that operates under a similar premise is clinicaltrials.gov where sponsors of clinical trials, whether they are industry-run trials or government-funded trials, enter information about those trials into a database that is run by the National

Library of Medicine and the Library does not attest to and really cannot attest to the accuracy of the submitted information. That said, because the Library has all of the publications and other genetic databases affiliated with it, I think there will be a natural way by which people will be able to assess, in a fairly straight-forward way, whether or not there is something really amiss in the information that was entered but we will not be curating this.

DR. FERREIRA-GONZALEZ: There is a big difference between clinicaltrials.gov where people get information about current clinical trials that are ongoing versus the Registry with genetic testing where people are going to start ordering the test and act on that. So it is very important to have in mind that people might have a sense that it is -- this Registry is in NIH, that it might be actually backed-up scientifically by NIH. It misleads the public on that particular issue.

DR. HUDSON: Right, so there is today a Registry that has a more limited set of genetic tests in it and I do not believe that the information is -- and that is run actually out of the National Library of Medicine as well, GeneTests.

DR. FERREIRA-GONZALEZ: Yes, I am very familiar with it.

DR. HUDSON: And it does not currently go and

double-check with the laboratories about the underlying validity of the submitted data.

DR. FERREIRA-GONZALEZ: Well you only put the name of the test that you do there, there is no other information. So when you start putting other information about analytical sensitivity, specificity, it is a very different --

DR. HUDSON: Right and I think actually the analogy to clinical trials is actually a good one. So in clinical trials you have to submit the result of your clinical trials and we are relying on people to submit the results of their trials and do it in a way that reflects integrity and honesty and straight-forwardness. I imagine that there are some, even in the clinical genetic testing arena, there will be a high incentive to submit accurate information and not mislead the government by submitting inaccurate information. I am sort of an optimist so I am going to look on the bright side.

There is also the ability, of course, for people to identify if there is erroneous information there and publish about it. And because all tests that are entered into the Registry will have a unique identifier associated with them, any publications about that test will be linked to that test entry. So if three people publish data showing that Test A actually does not detect whatever it is supposed to be detecting, that information will become affiliated with its record. So I think there is going to a process by which it

will be self-improving.

We do not have, even though I published an article arguing that we did have the clear legal authority to require, to mandate, the submission of information and then the ability to go and bop people over the heads if they do not provide correct information, we just do not -- that is not what we do at the NIH.

DR. FERREIRA-GONZALEZ: And then the issues of the data that you are going to be requiring, I think it will be very important to seek public comments on that. One of the areas of concern might be clinical utility because how do you define, first, clinical utility; what is the evidence needed to determine what clinical utility is? And if the information is required and not available, we might provide also more harm to the patients because that information might be misused or construed that the test is not good even though sufficient evidence -- or the evidence is not within the realm. So I will ask you to look at what information you are going to be requesting and what will be the consequences, unintended consequences, of having that information.

DR. HUDSON: And I am going to ask you to tell us what you think would be useful information to include and where certain kinds of information might be either burdensome for the submitter, which is an important criteria, or where that information will not be useful to potential users of the

database. So we are really looking to you to tell us what you think in terms of where information would be difficult to produce and then not that valuable at the end of the day.

DR. FERREIRA-GONZALEZ: Are you asking our committee to do that?

DR. HUDSON: I am asking the public, of which you are a part, to do that.

DR. TEUTSCH: Paul and then I have Mara, Sam, Jim and Marc.

DR. BILLINGS: Kathy thanks for a great talk. I have learned that there are Stanford students who also are seeking to have their personal genomes analyzed, so I just want to be fair to the Bay Area institutions.

The VA has started their Million Veteran Project and I am curious about how the NIH programs and the VA programs will communicate, interdigitate, and learn from each other.

DR. HUDSON: So that is a great question. I have just been put on the advisory committee that advises the VA on the Million Vet Program, whatever it is called these days, and so that is one mechanism of interaction. And certainly at the highest levels, we have been keeping in touch with and coordinating with the VA as well as other science and health agencies across government.

On the Registry we would certainly seek the VA's input; but I think the more important coordination is in the

actual conduct of their study, where we are trying to help them out to the extent that we can and also learn from them because we are doing other large cohort studies as well, the National Children's Study and other large studies, and so we want to be able to learn from each other.

DR. TEUTSCH: Okay, Mara.

MS. ASPINALL: Again Kathy thank you and I really appreciate the context of the broader picture and then coming to the Registry and other personalized medicine-related issues.

One of the issues that this committee and more broadly the industry has discussed is genetic exceptionalism and how the perception of that has changed as genetic tests -- not even getting into the issue of definition because we will be here all day. How do you think about that? How did you think about that in putting this Registry together specific to genetic tests?

DR. HUDSON: It is a good question. If you look at the total number of tests out there, coming up with an accurate number is a little difficult. But maybe you would say there is something on the order of 5,000 to 6,000 distinct tests out there, and I am making that up. And if you were to -- what proportion are genetic tests, there may be 2,000 or 2,500 or something like that.

So I think it is an interesting question to pose of

whether it would be useful to expand this Registry to be a clinical test registry rather than just a genetic test registry. And in fact comments on that subject would be welcome. I think there is a little bit of a notion right now that we do not want to bite off more than we can chew and hope we can start with a defined set of tests that we are more familiar with and that might be an easier way to go and then maybe expand later if there is interest in doing that.

DR. NUSSBAUM: Kathy thank you for this comprehensive review and it certainly is an exciting time and we see that enthusiasm on your part.

The question that I have is the genetic testing, particularly as it continues to expand, may be somewhat different than most diagnostic tests which are ordered by health professionals after a review of information.

And to build on Andrea’s point, do you believe that there needs to be a special sort of Registry provided to consumers because so much of this may be marketed directly to consumers going forward. And the reason I say that is because with this information, as we are going to talk about over the next two days, it may guide people in directions that even clinicians will not have clarity. And although clarity will be identified in the future, I just think that consumers may benefit if they have a trusted site to go to where they can have this information laid out to them, both the promise of

genetic testing and personalized knowledge of medicine and what we do know today.

DR. HUDSON: Yes, I think that is a good point and it will be a challenge as we move forward to see whether or not we can meet that need as a part of this Registry or if something else is needed.

I think understanding what consumers who are purchasing, especially direct-to-consumer tests, understand about the test that they are ordering and what actions they are taking based on those results is an important question. And in fact before I left Johns Hopkins, I was involved in designing such a study which hopefully my colleagues there will be reporting on before long because they have in fact surveyed the direct-to-consumer company's customers and specifically queried how much do you understand, what did you do based on that information, et cetera. So I think that will help inform us as we move forward.

DR. EVANS: I just wanted to amplify something that Andrea said. I think it will be really important going forward with an essentially uncurated database where you are relying on people to fill in fields to make sure that those fields do not try to capture more than they can. And what I am getting at there is it is one thing to ask for analytical validity and that seems reasonable and seems verifiable by the mechanisms that you mentioned. Clinical utility, of course,

means as it should, which is different things to different people. In the end it is an iterative and interactive process between clinicians and patients.

So I would just advocate being very careful about trying to create a field that is really undoable, unfillable, right. So I just want to, in the spirit of not biting off more than we can chew or consume, I think that trying to think hard about what the limits, what the real limits of this are, is really important to making it work.

DR. HUDSON: Yes and I think after we have a basic structure laid out, it is going to be really critical to partner with laboratories with a subset of well-defined tests and sort of try it out.

DR. EVANS: And clinicians, right. I cannot emphasize enough that much of where the rubber hits the road in the utility of tests be they genetic or what have you. I think that clinicians need to be involved if nothing else because they are the most direct representation of patients.

DR. HUDSON: Yes and I should say a word about that. The National Library of Medicine Center for Biotechnology Information has an advisory group that includes clinicians, medical geneticists and whatnot who will be providing input and oversight for this Registry as it moves forward. And in addition we are putting together a group from across the NIH where of course there is a great wealth of research expertise

and clinical expertise in a range of fields and we will be pulling together experts to advise us internally, as we move forward as well, so we make sure that we are not missing any of that insight; but thank you for pointing that out.

DR. TEUTSCH: I wanted to say to Jim that there are certainly groups that review these things, professional and other organizations, and it seems to me that one could include those kinds of things on a website so that you have the information.

DR. EVANS: Yes that would be a mechanism. It runs the risk, however, when you try to capture very broad things in discrete fields in a database, of being so all over the map that it becomes pointless. I am just saying to think hard about what fields make sense to actually try to include.

DR. TEUTSCH: Of course it is the utility that people really need to know.

DR. EVANS: Well exactly but that does not mean it is easy, right?

DR. TEUTSCH: That is why we have people like Kathy working on this.

DR. EVANS: Just because that is the most important thing, it does not mean it is easy and it can be fitted pigeonholed.

DR. WILLIAMS: So I wanted to comment on the last bullet of your last content slide. I am very curious about

your thoughts on the effective system to manage conflicts.

DR. HUDSON: I will just delete that bullet.

DR. WILLIAMS: I know you would like to delete that bullet but I noticed it unfortunately for you. But I think it is a very important issue because obviously there are a lot of stakeholders that come from a lot of different perspectives. And I am curious if you have some ideas about who needs to be at the table, what sort of fora would be needed to do this, and how this could be adjudicated. I think it is a really interesting thing to actually articulate and put up there.

DR. HUDSON: I think the issue of managing conflicts sort of surrounds the whole enterprise and especially if we are going to really effectively engage in moving things down this translational medicine pipeline, we are going to have to work really closely with industry and how do we do that and yet not lose the trust of people who are supporting the science.

So you may know that we have put out proposed new rules for governing financial conflict of interest of funded investigators. We have not yet gotten the comments in for that; it is out for public comment now. In those proposed rules we lower the dollar amount that is subject to disclosure which will probably be inconvenient for many. I know when I came into government and had to disclose everything under the sun in order to join the government again, I found it very

inconvenient and you certainly have made those disclosures in being a part of this committee.

But the notion is that sunshine is a good disinfectant and hopefully if we get these rules right, we can balance the need to work with industry and maintain the public trust because all of that information will be easily accessible and disclosed and managed, hopefully, very effectively. We have had some pretty egregious cases over the last several years in which NIH funded investigators have failed to disclose enormous sums of money from the pharmaceutical industry and that has not served us well and so we need to sort of clean up our act and we think we are on the way to doing that with these new conflict of interest rules.

DR. TEUTSCH: Great, any other questions for Kathy?

(No response)

DR. TEUTSCH: Kathy thanks so much. We are really delighted to see all this work going forward. Obviously you were an important part of this as we were putting this together and it is terrific to see all of it going forward. Clearly a dynamic environment and one which we sorely need this information and a good critical process for getting things from the laboratory into practice and used right so thank you for all that important work we really appreciate it. Thanks for coming.

DR. HUDSON: Thank you.

(Applause)

DR. TEUTSCH: I am going to turn at this moment to Marc Williams. You will recall in February we had some discussions about clinical utility and where we need to go. We have progressed a bit since then and we hope to have a larger session in October, but Marc, I think if you are prepared to fill us in on what has happened since then and what we should be thinking about as we move forward.

Update on Comparative Effectiveness Research

by Marc Williams, M.D., FAAP, FACMG

DR. WILLIAMS: Thanks, I am semi-prepared. I was sort of anticipating that the space might come tomorrow and so I had asked Darren actually to try and get some additional information for me but I think we can probably fumble our way through this.

So as Steve mentioned, there was a request at the previous meeting to kind of do a little bit more, laying back on our work on comparative effectiveness, to kind of get a sense for what some of the activities were going forward.

Behind Tab 10 you will see a Report on Obligations, Expenditures, and Unobligated Balances for Comparative Effectiveness Research. And as I reviewed that, I thought it was quite useful in terms of kind of getting a sense for where things are.

In the presentation that I gave in February, I gave

some ideas about where NIH was expending some funds related to what could be characterized as genomics and personalized medicine as well as where there are some infrastructure things that are being funded through AHRQ that could potentially benefit genomics and personalized medicine. But at that time we were waiting for a more formal announcement from the Secretary's office about the discretionary funds that were given there.

So I want to walk briefly through the report just to highlight a couple of different things. In terms of the AHRQ activities, they have indicated that they are funding efforts that are involved in horizon scanning, evidence gap identification, evidence synthesis, evidence generation, dissemination and translation, and research training and career development.

They have a total of $300 million and as of the end of March; they have allocated or obliged $54.2 million. They have an unobligated balance of $245.8 million. However, virtually all of that money is in fact in the process of being obligated in that all of their funding announcements for these funds are closed and there is nearly $200 million in research grants that are currently in the review stage. So they are anticipating that these grants are going to be announced in July and we will have a better sense of what exactly AHRQ is going to be doing in the space after July.

NIH is arguably somewhat farther along, in that out of its $400 million it has already obligated nearly $200 million with another $200 million in unobligated balance. However, as with AHRQ, basically they are through all the announcements and have done their reviews and are basically in the final stages of making the awards.

On Page 4 of that handout there is an outline of how they are doing and how they are spending the money. Of the $58 million that they have that is not committed, they are going to be spending $10 million on methodology development in comparative effectiveness research which I think would be of somewhat interest to this group.

I also again wanted to highlight on Page 5 that at the presentation that I gave in February, I indicated that there were I believe seven awards in cancer genomics that had come out of the ARRA funds. And as part of this, they are actually now starting a Center for Comparative Effectiveness Research in Cancer Genomics, so-called “CancerGen,” and it may be that we could prevail on Muin if he is still around somewhere -- oh there you are in my blind spot, to comment a bit on that when I am done talking.

So that has been the most tangible evidence of commitment to some monies going into the comparative effectiveness of genomics and personalized medicine.

The last funds are those that are the discretionary

funds to the Office of the Secretary which again total $400 million. The Secretary's report which begins on Page 6 outlines, I think at a relatively high level, what the Secretary is planning to do with those funds. But at the present time there is not a lot of detail relating to what is planned there.

And if we look at how the monies are allocated, the Secretary has actually expended only about $10 million of the $400 million to this point. Part of that related to some review that had to go through other groups at the administrative level before they were able to release funds. But as is noted in a number of these, shockingly I think to most of us, it is much harder for the government to spend money then we sometimes think it should be or think it is.

But as of March 31, the Office of the Secretary still had an unobligated balance of $388 million; so nearly all of the funds were unobligated. $246 million of this have actually been put out into funding opportunity announcements, both grant and contract, and those are now closed and in the review stage. That was what I was asking Darren to try and find out more information about because I was not actually aware of or somehow missed those announcements and so I am very interested to know what those were and what they were specifically looking for.

There is $53 million worth of funds that are in

announcements that are currently open and I guess I am probably even more interested in knowing where those are since they might be things that I would be interested in applying for.

And lastly, and I think of most relevance to our committee, is that there is $85 million in funding opportunities that have not yet been posted.

And so as I was thinking about the role of the Advisory Committee in this effort, it seems to me that we could potentially make some recommendations to the Office of the Secretary about how at least some of those remaining unannounced funds could be allocated to work in the genomics and personalized medicine space.

And as we were sort of brainstorming ideas in anticipation of the meeting, there are some themes that have emerged from previous reports from the committee that I think we could bring into discussion. Things like how do we determine evidentiary standards? How do those standards vary depending on if we are dealing with a rare disease versus a common disease? How do we set bars for information that needs to be accrued relating to genetics and genomics subgroup analyses? So more methodologic types of things.

And I think another area that would be of potential value, is again a discussion that we had a lot of last time and will be continuing to some degree in our next session,

which is about the informatics infrastructure and the monies that are being devoted through the HITECH Act and others towards meaningful use and things in electronic health records. And how the presence or absence of the ability to capture information relative to genomics and personalized medicine might be of some importance and how we could look at the impact that those types of infrastructure decisions could make on our ability to do comparative effectiveness research in this space. And I am sure that others around the table have a number of other ideas and I am looking to Sarah and Steve. Did I miss anything from what we had talked about in terms of possible opportunities?

Question and Answer Session

DR. TEUTSCH: No but I think what is important is the money that you are talking about all has to be expended by September 30 so there is a very narrow window for that.

DR. McGRATH: Expended or obligated?

DR. TEUTSCH: Obligated. So whatever mechanisms we are going to use have got to be done. But of course that is not the end of this whole issue because we are going to have the PCORI, the Patient-Centered Outcomes Research Institute, which is going to be created and is going to need to carry on this work. And there is a lot of work going on; I think there is a notice also about a meeting at ECRI this fall on the interface between personalized medicine and comparative

effectiveness. Although we have a specific opportunity right now, the window is very narrow. And I guess the question is Marc if we are going to do something, we will need to do something tomorrow, so we need something really drafted and I am not sure exactly what that would say at the moment. Do you have a specific proposal?

DR. WILLIAMS: No.

DR. TEUTSCH: Does anybody have a specific proposal that they want us to get in? Because I think we will be taking up the whole issue of clinical utility and comparative effectiveness probably in October as we talked about because we deferred it at the moment. But before we decide not to do something, Marc and Muin if others want to say something -- Marc go ahead.

DR. WILLIAMS: I said no but I think that there are things -- well no I really didn't mean no. I am thinking about the fact that drafting something would basically mean me drafting something and by tomorrow, neither of which are feasible. However, I think that there would be opportunities to take suggestions that we have made from previous reports relating to some of the things from our Oversight Report that would directly impact. And so I think we could potentially repurpose some of our existing recommendations into something that would be semi-coherent that could potentially influence the announcements relating to that last $85 million that might

be actionable by this group by tomorrow.

DR. TEUTSCH: Right and we have the letter we sent to the IOM some time ago when they were working on comparative effectiveness as well.

DR. WILLIAMS: So we have weighed in on this and we could probably pull something together that would be reasonable.

DR. NUSSBAUM: It is my understanding that the Institute of Medicine was charged with prioritizing CER and they came up with a list of a hundred as we know. And I just wonder, Marc, if we have cross-walked that list of a hundred top priorities to our thinking? And then secondly if we have or we have not, there may be a list of number 101 to 500 that could accelerate us taking work that was done by IOM in a very broad context of exploring ideas with many.

DR. WILLIAMS: So let me respond to that. We did in fact cross-walk both the IOM Report and the FCCER Report both of which were meant to be considered by the Secretary as she looked at allocation of funds. There was less from the IOM Report, other than in the oncology realm, which could be directly purposed toward comparative effectiveness research.

And the Secretary has essentially said that the monies that are under her discretionary power are going to be looking less at these articulated projects for specific disease entities, which is what the IOM Report essentially

weighed in on, and is going to be looking more at issues of infrastructure and methodology which were more covered in the FCCER, I may have left a C out there, report and that seems to have been, in what I have seen from the Secretary, where that focus has been. But we did look at those and those are issues that we could put forward and that is why I was suggesting that the infrastructure emphasis may be the way to go.

DR. KHOURY: So much talk about this topic here but since Marc mentioned some of the NCI projects, last year as I spent a lot of time at the NIH, right now we are able to use some of the ARRA funding to fund seven groups in genomic and personalized medicine. And what these groups are doing in the next two years, and there is a very active agenda right now including the CancerGen project that you mentioned, is setting the groundwork for sort of evaluating the clinical utility of genomic and personalized medicine.

There is both knowledge generation, knowledge synthesis, methods development, as well as trying to figure out sort of using modeling and other approaches, working with the EGAPP working group, ways to accelerate the evaluation of clinical utility. So in this context, this will all be good.

I think as time moves on and post-ARRA with this PCORI institute and the emphasis on both translation and now the personalized medicine, it looks like CER is one mechanism to do a lot of work in genomic medicine because not all

genomic applications will end up being subjected to randomized clinical trials. Many of them are already in practice or will be in practice so this would be one way to get the information in a useable fashion.

Just one comment on the Genetic Test Registry, I should have made that comment when Kathy was here. I think as people have been saying in the Q and A section, the information that is part of the Registry will have to be looked at using independent bodies such as panels like EGAPP and others especially from a clinical utility perspective.

And I think having these academic groups working, both generating the evidence on clinical utility and validity as well as synthesizing the evidence, will become part and parcel of this Registry.

So I just sent Sarah an email as part of our GAPNET Initiative. I wanted her to share with the group what the recent offering of the CDC has been which is the GAP knowledge base which is already online as of last week. And the way I envision this is it would go hand-in-hand with the Genetic Test Registry. So once you all get that email, you can surf the web and look at some of these goodies, thanks.

DR. TEUTSCH: All right, so Marc do we have something we can -- I mean we can certainly remind the Secretary about things we have already done. Is that sort of what you think we should be doing at this stage because she

already has those presumably sitting on the front of her desk?

DR. WILLIAMS: Right, but what she did not have when we sent those that she does have now is $85 million that she could actually devote to them should she choose to do so.

So yes, as I think about the process and the fact that this is a deliberative group, to understate the case dramatically, to come up with something de novo by tomorrow that the group could actually agree to and forward, I think is unrealistic. But if we take things that the group has previously agreed to and say this is something that could be purposed within the context of comparative effectiveness research, I think that would be valuable to try and frame the discussion about the remaining announcements.

DR. TEUTSCH: It seems to me, because this has to be done pretty quickly if we are going to have any effect, we could write a short cover letter that would basically take the documents that you talked about, the Oversight Report, the letter to the IOM, and there was one more which escapes me at the moment and basically transmit them to her with a reminder that they have important recommendations that could inform her decision making.

DR. WILLIAMS: I think the other document that we could probably salvage portions of would be the comments that we submitted relating to meaningful use because within those documents there is specific verbiage about the use of

information to do genomics and personalized medicine research.

DR. TEUTSCH: So let me just get a sense of the group. Is that something that you all think would be useful? We can do that reasonably quickly and I think we can do it pretty much offline if that is -- anybody think that is not a useful thing to do?

(No response)

DR. TEUTSCH: All right we will take no comment as assent. Any other further thoughts on this?

(No response)

DR. TEUTSCH: All right, well thanks Marc we appreciate this. Sorry to put you on the spot. And I think we will be hearing a lot more about clinical utility and actually of some of the things Muin was referring to about where the field is going and some of the things that we may want to react to in the Fall.

While Kathy was speaking I saw David Hunt coming in -- he is still over there; he has moved. And I think with your permission, it is probably just as well David if you are willing, we will do you before the break rather than afterwards. It is great to have you here.

We had the pleasure of hearing from you before, I think it was at our last meeting, and obviously we have responded to some of the things from ONCHIT which is really important. So we have invited David back to actually give us

an update on the Interim Final Rule related to electronic health records and he will be discussing the development of guidance on de-identification, the ONC Commission Safe Harbor De-identification Project and their efforts to promote data security to ensure patient privacy.

David is the Chief Medical Officer for the Office of Health Information Technology Adoption and ONCHIT. It is always great. We were very illuminated by your last presentation and look forward to more of the same so David thank you very much for coming here and we appreciate it.

Updates and Developments from the Office of the National Coordinator for Health Information Technology

by David Hunt, M.D.

DR. HUNT: Thank you very much. We at ONC are very, very grateful for the opportunity to provide this incredibly important group an update of our activity. When we were last together, we met at the start of quite a remarkable streak of winter weather here in D.C., that time really tested the city. It really bore out the statement that John Kennedy made about our city before, that D.C. is notably a city of Northern charm and Southern efficiency.

(Laughter)

DR. HUNT: While I do not know if we are more charming or really any more efficient at ONC, we have been doing our best to be responsible stewards of the incredible

trust that was placed in us. But before I go to a tape of our highlights, if you will, of what we have been doing since we last met, let me give a quick recap of what we discussed before.

(Slide)

I pointed out that tremendous responsibility and trust was placed in ONC with the HITECH Act which is a section of the American Recovery and Reinvestment Act. Now it seems that another one or two small pieces of healthcare legislation may have passed in the 481 days since this came to a conclusion, that is, the HITECH Act. So to that end, our hopes that HITECH was a prelude, if you will, to significant healthcare reform have really been answered. And while we have a few important responsibilities within the new healthcare reform legislation or the law, we are still pretty centered on the tremendous amount of work that we were given with this legislation in 2009. Still I will be the first to admit that this form that I presented before is a little bit more confusing so I am always thankful that Dr. Blumenthal was able to articulate clearly our priorities in four simple concepts.

(Slide)

In HITECH as we discussed before, those priorities are to define what the meaningful use of an electronic health record is; we are going to support the medical community in

meeting that definition. Once more we plan to establish a public trust which is so very important in a healthcare system that actually leverages to the full extent information technology, and finally we want to make sure all of our work helps to foster greater innovation in this field.

(Slide)

And to that end, this is a very high-level view of our operations in which we plan to have the adoption of electronic health records as well as the exchange of information all feed into the meaningful use of electronic health records. And the final goal, as you can see, is to improve individual and population health outcomes, to increase transparency and efficiency, and to improve our ability to study and improve healthcare delivery. And finally at the bottom undergirding all of this, we plan to continue to foster innovation and promote research that actually improves our ability to use this technology as well as the technology itself.

(Slide)

Now to that end I will pick up in terms of the highlights. I am not sure if we were able to share very much about this at our last meeting. This has been a piece, for lack of a better term, the R&D work if you will that we are trying to catalyze in terms of advancing our knowledge base and how we are able to leverage this technology. This is

called the Strategic Health IT Advanced Research Projects. We are trying to get some play on the DARPA, I think, acronym from before. Please note that that investment of $60 million actually was the entire size of our 2008 budget. So we have come quite a long way.

(Slide)

Now with the Strategic Health Advanced Research Projects seen, we have a number of institutions of higher learning that have formed and coalesced around four large groups of projects. Security of Health IT, which actually remains of fundamental importance to all of our work. Cognitive Support, how do we actually help leverage information technology to be, for lack of a better term, a cerebral assist device in the delivery of care? We have to learn more on how to optimize the healthcare application as well as network platform architectures. And finally we have to help enhance our ability to use the information that we have in more than one form or for more than one purpose.

These are just the lead organizations, the lead institutions, as well as the lead researchers, investigators, for this work. I should point out that each of these four areas with their leads are actually working with about a dozen other institutions and researchers so this really represents a good cross-section of the United States health services research and medical informatics communities.

This work has two major deliverable schedules. The first is for short-term deliverables. And it is a bit quixotic and please bear with us. When you are talking about research and short-term deliverables most would say, “oh that is five to ten years” but actually our short-term deliverables is about one year in terms of we want these groups to have some significant milestones met after one year. And most of those are dealing with some of the known specific problems that we currently have.

In long-term deliverables, the second large set of deliverables, we were thinking on the order of about four years or so that they will be able to produce some results and inform us on how to actually improve health IT systems.

You can keep a close eye on this work as well as all others through our website and I will give the URL for that in just a minute, toward the end of my presentation. But I should also note that this group will be regularly updating the Health IT Policy Council which is one of our two main advisory committees that meet on a monthly basis. So please look out for the results of this work as we are continually updated with that.

Now having said that, to look at the research portion and our ability to innovate, I have to get back to the sort of nuts and bolts of what we have been doing.

(Slide)

To that end, one of the biggest pieces of work are centered and focused around the meaningful use, as has already been mentioned, of electronic health records.

I purposely, for this presentation, have very little information specifically about the final rule regarding meaningful use. I mentioned earlier that that is going to be released in the late Spring and everyone is saying "well you are here." We still have a few days left of Spring and we are actively working but we expect to meet our timeline, plus or minus one or two weeks let's say, for the final rule with regard to meaningful use.

And just to remind everyone also, that rule will actually speak primarily to the expectations around the meaningful use of electronic health records for the 2011 period, sort of our starting period. And we all recognize that that has got to be a bit of a special time given the relatively short period of time we have had to ramp up all of these programs. And the goals and the expectations have to be appropriately managed. With that regard, the rule may speak to some of the expectations for the second and third periods of meaningful use which are 2013 and 2015 respectively and will be able to sort of outline or frame out what some of the trajectory will be toward that end.

Now as one of the important pieces to supporting meaningful use, you will notice my previous slide highlighted

the fact that an exchange with some of its components, namely standards and certification, have to be a huge support for that work and we have released an Interim Final Rule which set an initial set of standards back in December, shortly before we met, that discussed basic functionality, interoperability, and the security of health IT that will be used to support meaningful use. And the expectation is that we will have a final rule coming in very, very close proximity, perhaps before the actual meaningful use rule is released. And that set of standards and certification will really be what is used to help support all of this work for this initial period.

You will also notice that in March we were able to release a process for how the certification of these records will proceed. The HITECH Act is complex but is incredibly elegant in some of its goals and that is, it has given ONC a dual responsibility. One to create the set of standards and if you would the requirements that will serve as a base for all electronic health records as well as we have taken back the control of HHS, the overall role of overseeing the process of certification.

And to that end, we will look to accredit a number of entities, not just the one that was present before in the form of CCHIT, the Certification Commission for Health IT. But the expectation is we will have a number of entities that will come and be able to do this work to provide increased

capacity as well as some specialization, as a number of different groups have indicated we need to have, to certify that these records actually meet the requirements. And so you will note that the Interim Final Rule was passed and the final rule will be coming out, as I said, in close proximity to the final rule for meaningful use.

(Slide)

One thing that I like to point out, and this is incredibly important particularly for a number in the community that have asked about what the electronic health records will mean for those perhaps who are disabled or in some ways underserved. And we like to point out that within the Interim Final Rule, we did highlight that nothing required by the Interim Final Rule, and the expectation will be that that will also hold for the final rule, should be construed as affecting our existing other legal requirements under federal law; so all important regulations, rules, and laws that are meant to assist compliance in access to the healthcare system will still be in place as a result of our actions there.

(Slide)

Now I think I did highlight some of this before but again so much of our federal procurement rules handcuff me in being able to say things before they are actually final. And I know that when we spoke before, the concept of Beacon Communities was right on the cusp of being released and as you

can see, on the cusp in February turned into the first week in May. But on May 4 the Secretary and the Vice President announced 15 Beacon Communities that have been given resources to actually affect what we like to think of as the full flower of what health IT can mean to the medical and healthcare communities.

These communities, just to recap, in the applications have to demonstrate that they are a little bit more advanced if you will in terms of some of the infrastructure and basics around leveraging health IT. So they would automatically -- they would have high adoption rates and they have an infrastructure in place but most importantly they have a culture that actually embraces and is looking to actually leverage health IT to a greater extent.

To that end, these communities have already set up or have made significant progress in having all of the important stakeholders at the table to actually speak to how they will be able to most effectively use information technology.

With all of this elegance and efficiency, there are a significant number, or there are a number of defects in the HITECH Act. One of which is it does not speak to the entire continuum of the healthcare community. Many specialized groups did not see themselves as being able to have a piece of meaningful use and/or some of the incentive programs. To that

end, I look toward the long-term care community, home healthcare, and some in the mental health community in some aspects. There are a number of different constituencies that really were not as fully fledged out as say primary care and the traditional allopathic medical specialties in the HITECH Act.

The Beacon Community Program is expected to remediate many of those defects in that these resources were targeting communities that again were a little bit further advanced. To that end, I like to think of them as sort of our A students. And the expectation is that they have everyone at the table, long-term care, full-fledged nursing, all the spectrum along the continuum of care and we were asking them "what could you do with additional resources to really leverage all that can be done with health IT?" And we are very, very pleased.

And once you see some of the communities that we have, I think that you will be pleased also with some of the responses that we have. Most all of my slides, I should point out, are taken directly from our website and again the URL will appear at the end of my presentation. I did that on purpose to make sure that we really begin to let everyone know that virtually everything about what we do will be able to be found in greater detail in our website.

(Slide)

These are the communities that have been awarded the Beacon Community resources and you will see that they are a very wide range geographically as well as the types of delivery systems. So you will see Tulsa, Oklahoma and Brewer, Maine. You will see Salt Lake City and San Diego. You see Hawaii and Buffalo. So it is a very, very interesting and diverse group and I would encourage all of you, again, with any interest in the Beacon Community Program to go to our website. Descriptions of all of the work for each of the communities are on our web page and I think that you will be able to see that these represent really a very exciting group and we expect a great deal from them.

I should note also a couple of interesting points. The first is that we have realized that we have resources to fund two additional Beacon Communities. So while we have fifteen, the expectation is that we will be able to fund two more and so that process is in the works; so we have two more that will be coming out.

As well as the fact then, and it sort of rode a little bit under the radar when we first announced the concept, and that is that the VA and the DOD are working together actually in a somewhat parallel program around the same concept of Beacon Communities. The nuance facets of procurement in the VA/DOD system versus HHS really meant that we had to go along parallel tracts rather than completely

integrating these programs. But the later expectation is that we will be able to leverage the information from the VA/DOD Beacon Communities. And I believe they are going to be funding a total of four and I believe two have already been announced. We will be able to leverage the information and the results from them just as well as we do from our own HHS-funded Beacon Communities.

(Slide)

Back to some of the nuts and bolts pieces, I tried to go with something that is incredibly exciting and a little less -- almost as exciting let's say and that is our Regional Extension Center Program. That actually is -- if you have to think of a centerpiece to all of our work, I would say that is it. It is a little bit self-serving because that is the group that I am in that is running this program.

The Regional Extension Center Program is a group of now 60 centers throughout the country that will be providing the technical assistance to, boots on the ground if you will assistance, to practices and providers to attain the meaningful use of electronic health records.

These groups will contain an eclectic staff of folks understanding the nuance of security in health IT networks, the software as well as, and most importantly, the steps that are needed to take a practice through the total transformation that is the result of really having an electronic health

record in place.

So to that end, they have individuals that are skilled in the nuance of guiding practices through how to have patients flow through your office now that you have a completely electronic office setup. So they are providing, again, the boots on the ground technical assistance to providers.

The goal is to have over 100,000 providers through these programs attain the meaningful use of electronic health records. I mentioned earlier that when we last spoke we had announced 32 of those grantees and since that time we have been able to announce another 28. The total funding for this program is on the order of about $600 million.

We have a great deal of high expectation for these centers in being able to be the centerpieces and resources in their medical communities on how to actually attain the meaningful use of health IT. So they will be the local experts. This program was somewhat a derivative of the Agricultural Extension Program that many of you may know something about in where we have actual local experts that are able to help guide individuals with their agricultural needs.

(Slide)

Now one thing that I like to point out about our Regional Extension Centers, they really have a charge to obviously provide resources and expertise throughout the

medical community but they are specifically charged to target and work with those providers who are probably least likely to be able to do this on their own. By that I mean small practices; practices with ten or fewer physicians or clinicians. Practices in rural environments; hard to reach locations. Practices that are serving the underserved communities; those who are basically with a waiting room full of patients and very, very little time to go through a twelve step program in how to change and transform their practice. And those are the individuals that these centers are specifically going to be working with.

I should also note that in addition, since our last announcement, while we did have resources to have these extension centers work obviously with individual practices and also hospitals, since we last spoke we have been very pleased to announce that we have been able to add some additional resources to have these extension centers work a little bit more closely with critical access hospitals.

I am not sure how many of you are familiar with critical access hospitals but they are as their name implies, they are the small hospitals usually out in relatively remote areas, traditionally very, very small, but they provide a key critical link to healthcare services throughout this country. They are the place to go in many places in the more rural areas and they are sort of, if you would, an island in the sea

that so many of these communities depend on. And we recognize that they above probably all others really, really need to be able to leverage health information technology to its fullest. So we are very happy that we have been able to add some resources to help the Regional Extension Centers work a little bit more closely with those.

That is a quick round-up of the things that we have been doing and I am hoping maybe we can have a bit of a discussion, questions and answers, as far as some of the other details about what we will be doing.

(Slide)

I always like to leave with a highlight and this is my highlight for today. We have been doing an awful, awful lot. In many cases some folks will assume that we are a bit lost given the magnitude, scope, and amount that we have been doing but we are not. We are not lost at all but we will admit to having been confused for a few weeks or so as we have gone along.

(Slide)

So with that let me stop and see if they have any questions. And again this is the URL. I really encourage everyone to go to this web page. You can sign up for our listserv; we have a variety of listservs that probably speak to almost every interest within this room. You can sign up for all of them or a subset of that and you will be among the

first to find out, for example, the actual minute that the Meaningful Use Rule is published or the final rule for the Standards and Certification as well as keeping up to date on so many of our other programs, so I highly encourage you to go and see us on this website.

Question and Answer Session

DR. TEUTSCH: Great David, thank you so much for the update. One of the things that we were hoping that you could speak to while you are here is some of the issues regarding de-identification and privacy.

We have a whole group working on general McDATA* sharing which is obviously a key interest to us and EHR is both an important mechanism as well as a challenge on this score. So I was wondering if you could, before we turn it open to general discussion because I am sure there are people who are interested in all aspects of this, if you could share a little bit about where you are with the de-identification, patient security issues.

DR. HUNT: I would be happy to. Getting back to the original HITECH legislation, one of the things that you notice is the first thing, first of our responsibilities, is to make sure that this information remains secure and is available to help support institutions of public health. And as part of that rule, the Act actually provided for the first ever Chief Privacy Officer at HHS. And we have been very pleased that we

were able to bring on board Joy Pritts who is an actual giant in the field of privacy and security to be the Chief Privacy Officer. Working with our group, she is the direct report to the Secretary. And with her leadership, the office has been able to begin on a series of projects to help inform our policymaking with regard to security and privacy and particularly the de-identification of information and then the secondary use.

On our website you will notice that we came out with a white paper in the middle of March which actually is a big framework for how we will begin to discuss and begin to actually frame out some of our policies around security and privacy and I refer everyone to that white paper. The Interim Final Rule around meaningful use will also speak to some of the aspects around security and privacy that are there.

The most important piece I think around security and privacy is obviously when we are discussing the exchange of information across and outside of a particular practice or a particular provider's purview. And to that extent the NHIN which is the National Health Information Network, a program that we had set up years ago and is actually being more robust now, has released a set of standards and protocols called NHIN Direct which actually is a baseline to begin to start to exchange and use some of this information.

And within those protocols you will see some

rudimentary and some very fundamentally important requirements around how data will be encrypted, how it will be anonymized, and how it will be actually shared. This is going to be a learning process above and beyond all else and we expect that Joy's group, over the course of probably this Fall, will be able to release a number of policies and policy statements with regard to specifics around data sharing and security with the expectation that we have a kernel that is sufficient to help support meaningful use by the start of 2011.

So you will see more and more coming out of the shop. We have a whole section on privacy and security policies moving forward.

DR. TEUTSCH: That is clearly an area that we will look forward to hearing a whole lot more about because it is going to be critical to helping people get the clinical utility out of this information.

DR. WILLIAMS: I appreciate the Boone quote. I must admit I operate under a little different quotation. The Japanese samurai philosopher Ikkyu said "having no destination, I am never lost."

(Laughter)

DR. WILLIAMS: However, I wanted to go back to your discussion around the Beacon Communities. And as you heard from us last time as well as in our written comments, as you talk about communities that may be feeling somewhat

disenfranchised from the overall meaningful use process I think we have communicated that we represent one of those communities as well. And I wanted to clarify something that you had said about the purpose of the Beacon Communities and then be a little bit more focused in my question.

It sounds like, from what you described, that the Beacon Communities are really being constituted to pull in more broadly a lot of these different areas to have discussions that are perhaps more holistic if you will. The question that I had is given that there are two available opportunities, are any of the Beacon Communities focused around one specific area of concern and if so or if not, would there be receptiveness from the Office of the National Coordinator relating to constituting a Beacon Community around issues of genomics and personalized medicine and other informatics concerns in this realm?

DR. HUNT: I would say -- and I am glad you asked that question actually. Each of the communities themselves were asked to speak to a broad range of inclusion and as you said, providing a more holistic approach. But each of them also is looking at a specific and specialized set of areas.

And I think to speak to the genomics and genetics piece, and I should have had that right on the tip of my tongue, but I believe the group at Rochester in the Mayo Clinic may have a little bit more of an emphasis on that.

Some of the communities are working to make sure they integrate mental health to a greater extent. Others are working in the area of health disparities. So each of the communities, while providing a broad beacon if you will of how we can actually leverage all of this technology, do have a somewhat specialized area of focus.

And if you go again to our website and click on any of the links associated with these various communities, you will see a full description of what their proposal entailed and why they were chosen to actually do this work in the generic sense and in the specialized sense of what they will be able to bring to the table in a specialized area. Some are working to focus on, as I mentioned, the underserved. One is actually focusing on the integration of long-term care within the community. Others, they have a very, very interesting and diverse group of specialized interests and so some of them do speak to some more specialized interests. And the final two that we will fund additionally also have that same aspect.

But all of them, the one defining characteristic among all of them, is that they have a very, very large table where virtually everyone in the community has a seat and is able to actually speak to how to better integrate this. Because the one thing that we know is that the delivery of healthcare and the advancement of medical science is not complete until you have everyone at the table, not just

specifically those involved in the practice of medicine but those involved and working on some of the social determinants, if you would, of healthcare. And these Beacon Communities, I think that you will be pleased. You will see that they speak to these issues in a very, very clear fashion.

DR. TEUTSCH: Mara and then I am going to ask Jennifer to speak a little bit to some of the privacy issues.

MS. ASPINALL: So David thank you very much for the very comprehensive presentation. Two questions; one is on interoperability. I mean that is one of the key issues that has been, and I believe will continue to be critical, in terms of not just for individual communities but given the nature of the beast whether it is individual patients moving, physicians moving, or changes. How do you think about that? What specific initiatives do you have to further that goal which was specified as one of the key issues of healthcare reform? And then I have a follow-up question.

DR. HUNT: Yes, actually if we do nothing else at ONC, we must be able to support interoperability. This is all and only about the exchange of information and the exchange of data which may actually lead to the exchange of knowledge; that is a high concept and we are not sure if we are going to achieve that. But we have a number of different programs and everything that we do really is trying to lead toward that end.

It has been pointed out that with our current rather haphazard system, if we do not affect interoperability, all we have done is place the system that we have in individual electronic silos that still will not affect the full flower of healthcare. So to that end, our Office of Interoperability and Standards actually is releasing the protocols on the standards and the expectation. And among those standards you will see expectations around the ability to exchange information.

The amount of information or the information that can be exchanged at the earliest level will be necessarily rather rudimentary. To that end, all certified electronic health records will be able to exchange information regarding a patient's medication, they will be able to exchange information regarding a problem list in allergies as well as a clinical summary. That is an early start but that is probably all that we could ask of the entire domain on such relatively short notice. But moving beyond that, we will have interoperability standards that will continue to come out and the best place to see those will be in the NHIN work.

MS. ASPINALL: So for instance with the Beacon Communities, might you have any pilots, for even them as the Grade A students, to be exchanging information and truly have Level 2 interoperability?

DR. HUNT: Oh absolutely and that actually is --

again being the A students, the floor, if you would, is the expectation that having everyone at the table, everyone would be able to exchange, share and use this information so we expect to see robust information exchange.

Many of the Beacon Communities, and I am looking toward Providence, Rhode Island, the community in Indianapolis, the Indianapolis Health Exchange, the community in Eastern Maine, are specifically -- they actually are health information exchanges so they will, above and beyond all else, but everyone expects that within these Beacon Communities that there will be robust exchange. If there is not exchange, then we do not have anything.

MS. ASPINALL: So lastly, one of the key pieces of that are the service providers, the vendors, industry, for profit and not-for-profit, you have not talked about that community. How do you interact with that community if at all to ensure that they understand your priorities, your focus? Any proactive, proscriptive programs with indeed the vendor and outside provider community, providers meaning IT providers not healthcare providers, how does that work?

DR. HUNT: That is an excellent question. In the lead-up to the Meaningful Use Rule we held a series of meetings with different groups and one of the groups that we specifically wanted to speak to is the vendor community, the HR and the IT vendor community; those actually building the

systems. And we listened very, very carefully to what they felt they are able to provide and what type of support and assistance they may need to be able to do this work and we took their suggestions under advisement.

And the Office of Interoperability and Standards, to a large extent, they are crafting the rules around the standards and requirements. And having worked relatively closely with the HR vendor community, when we spoke to the certification, when we learned more from the certification groups and CCHIT was probably in the fore-front as being the first out of the gate, they spoke to what we could expect as far as the first step in interoperability and standards. It will be a continuing dialogue. It has to be a very careful dance because with these additional resources we have to be responsible stewards of the resources that have been given to us and so we have to be prudent in the expectations that we have.

And when you look at the comments actually that came in from the vendor community for the Meaningful Use Rule, they were very supportive. We were very encouraged by the number and the breadth and the depth of the comments particularly from all segments but also from the vendor community.

And while this is definitely -- we have a number of aspirational goals; it appears as though we will be able to do this. We will definitely be able to meet our goals

particularly for 2011. And as you point out, the Beacon Communities, the expectation is that they will go a little further. Many of those communities have not dedicated or a smaller group of vendors that they are working with and I am thinking of the Mayo's, the Geisinger's, the Utah --

MS. ASPINALL: Ones that are in common.

DR. HUNT: Exactly. And we will see how far they can continue to advance this. And also again I come back to the NHIN work and particularly the NHIN Direct as that core set of standards and protocols that will be able to be used to share and send information back and forth and you will continue to see that grow.

We will have more information on NHIN Direct coming out over the course or the summer and I do not want to steal that thunder but I think that most in the community will say that we have a good start at being able to share and exchange information. And we have taken the advice and the words of the vendor community to heart in terms of what we can expect them to do.

But on the same token, it is very important that many have thought that some of our current circumstance may be because we have not been as focused as we could be in challenging the vendor community. So this, as you will see with the Meaningful Use Rule when it comes out, this is not going to be a short putt. It is going to be challenging and I

think a number of the pieces that you will see in the press have been speaking to that challenge. But to the greatest extent, I think we believe that the vendor community will be able to step up and that is fundamental; let's look at it very, very clearly.

Through the HITECH Act the vendor community is effectively having the Department of Health and Human Services provide incentives for their customers to purchase and use their services and products. So to that extent, a very high standard will be expected of them. And I think that we will see that they will be able to meet that standard.

Traditionally in the rest of the technology sector, those standards and expectations have been met and in many cases exceeded. I hold in my pocket right now a phone that is the equivalent of my desktop computer ten years ago so I think they will be able to step up and do it.

But also I should say that it has to be integrated and that actually is also some of what we expect from the SHARP researchers. Many of them are working particularly around the Harvard group platform architectures, how to exchange information, and they will continue to hopefully guide and give us advice and counsel on the best way to move forward.

MS. ASPINALL: On an integrated basis.

DR. HUNT: Exactly.

DR. TEUTSCH: Great, Sam and then Jennifer and then we will wind up this session.

DR. NUSSBAUM: David thank you for providing this sort of exceptional progress you are making. The question I have is if you look at the HITECH Act and other investments, it is somewhere around $40 billion in health IT, right, and so this is our rescue, right? We are all claiming that this will really improve the quality and affordability of healthcare.

So two questions are, one if you look at the Beacon Communities you are struck by -- these are communities that have made impressive advancements over the last decade and most of them are actually dominated by a single health system if you look at them, so you know Geisinger or others. And most, if not all, are in sort of secondary or even tertiary communities and markets. So the question is how do you get to the New York's, the Los Angeles', the other -- you know where people are living basically?

(Laughter)

DR. NUSSBAUM: And where care is not as highly coordinated, when you have Eastern Maine Healthcare System where everyone is owned by Eastern Maine Medical Center. And the reason I ask that is because isn't really our Holy Grail getting information to the point of care and how are we going to get drug information, lab information, and really decision support particularly in areas that are advancing rapidly like

molecular genetics, how are we going to get that information to the bulk of the practitioners, to the American people?

DR. HUNT: That is an excellent question and to that -- and I would point again to our Regional Extension Center Program. Our Beacon Communities, there are very few, 15, will be a total of 17, and obviously they cannot be that disperse. Although I will speak to a couple of the groups and mainly the Delta Health Alliance in Mississippi, they really are working. And if you read their proposal and what they plan to do, they really are speaking to making sure this is where people live as you point out.

But the Regional Extension Center Program is actually -- probably will meet the needs that answer your question more than any. They are the boots on the ground that actually are going to be working, hands-on technical assistance in the communities with providers to teach them first how to adopt, how to implement, and then exchange.

(Slide)

Within all of this, and I am sorry that I gave a too short discussion; you will notice that we have a whole section on health information exchange. We have a parallel program, again to the tune of around $600 million of state-based health information exchanges that are going to be working again closely with the Extension Centers and the expectation is that in each of these states, providers will be able to, through

the Extension Centers, learn how to adopt and implement this technology and then learn how to join and plug-in to, for lack of a better term, their state-based health information exchange and then begin to exchange some of this information.

You are absolutely right, many of the Beacon Communities, they have already actually done this to some extent and they are dominated by some significant forces each within their community -- well I will not even say each, many of them. Again I will point to the Delta Health Alliance. The Community Services Council also in Tulsa, Oklahoma is very interesting as well as the Western New York Clinical Information Exchange. So while your point is very valid and well taken, I think that we will see, even within the Beacon Communities, action where the people live.

But specifically the expectation is that the Regional Extension Center Program working in close coordination with our parallel program of health information exchange will be providing the technical assistance and the services to the majority, well over 90 percent; the catchment area for these programs is well over 90 percent of the population centers of the United States, to be able to get this in the rank and file healthcare providers to be able to do this.

But still with all of that, it is important to note that the Office of the National Coordinator was given about

$2 billion of resources and we are leveraging about $20 to $40 billion of incentive programs through the Centers for Medicare and Medicaid Services. And while that is significant, it pales in comparison to the goals that we are trying to accomplish. The resources required are much, much higher and we are hoping that we will be able to use the principles of Archimedes and use this as a lever to advance even further; because even with those vast resources, the inertia that we are trying to overcome is much, much greater.

DR. TEUTSCH: Jennifer, Office of Civil Rights works obviously a lot on the HIPPA Privacy Rule and in conjunction with colleagues at ONC; I wonder if you could share some of your thoughts about this?

DR. WEISMAN: Sure absolutely. So I can address briefly your question about de-identification. We did hold a two-day workshop earlier this year in D.C. on the topic of the de-identification standard and the HIPPA Privacy Rule. So we had a number of panels and public comment on a variety of topics. We covered the Safe Harbor Method and the expert statistical methods of de-identification and a number of other topics including re-identification issues, et cetera. The workshop is linked on our website. So if you go to OCR's Privacy website, there is a link where you can see the webcast of the workshop as well as the presentation materials that were there.

We will be issuing guidance on de-identification at some point in the near future. And there will be opportunity to submit comment to the new guidance.

And there was a link on our website and will be again if it is not currently there to submit comment.

DR. TEUTSCH: Is there going to be anything specific to genomics as part of that de-identification process?

DR. WEISMAN: That topic did come up as it often does in the workshop. I mean as you are aware, it is not listed currently as one of the 18 identifiers within the Safe Harbor Method and that is something that we are happy to receive more comment from the community on. So if you guys would all like to weigh in with your thoughts on that, we would be happy to hear that.

DR. TEUTSCH: Thank you.

DR. HUNT: If I could dovetail on that?

DR. TEUTSCH: Sure.

DR. HUNT: I am taking lessons from you on how to answer, that was wonderful. Giving all the information you can but then keeping it within balance; I need to learn how to do that. But HITECH also speaks to this important point, and we do not like to highlight this very much because obviously the governmental role, but it also speaks to the enforcement issue. And there have been resources provided toward the enforcement of privacy and security and the hope is that in

addition to the policies, the increased resources for the enforcement of privacy and security will go a long way.

DR. TEUTSCH: Well David, thank you so much for again joining us. It is obviously critical to the well-being of our healthcare system and the use of information so thank you so much and we look forward to having you back. I am sure we will be hearing more and thanks Jennifer for your additional comments.

(Applause)

(Luncheon logistics discussed)

DR. TEUTSCH: Let's go ahead and take a ten minute break and we will be back here at five of.

(Whereupon a break was taken)

DR. TEUTSCH: As I mentioned earlier, we are going to move on to the next session on CLIAC. Bin Chen from the Division of Laboratory Systems at CDC is going to talk to us about CLIAC's recommendations for good laboratory practices for biochemical genetic testing and we will have some time for discussion. I know she has some questions that she would like us to respond to. And this has been a topic of great interest to us and certainly a major focus of our Oversight Report on genetic testing so welcome Dr. Chen and we look forward to your presentation.

CLIAC Recommendations for Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening

by Bin Chen, Ph.D.

DR. CHEN: Thank you Dr. Teutsch for the introduction. My name is Bin Chen. I am from the CDC's new Office of Surveillance, Epidemiology, and Laboratory Services. And I need to say it is great to be here to update SACGHS on the CDC efforts to develop good laboratory practice guidelines for genetic testing.

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So for my talk I am going to highlight the recommendations provided by the Clinical Laboratory Improvement Advisory Committee addressing good laboratory practices in genetic testing particularly the recent CLIAC recommendations for biochemical genetic testing and newborn screening. And I will be discussing the development of CDC guidelines not only for molecular genetic testing but also our upcoming new guidelines for biochemical genetic testing and newborn screening. And then at the end, as Dr. Teutsch pointed out, we have some issues and questions for SACGHS input.

(Slide)

So just a brief overview of the current oversight landscape for genetic testing. The CLIA regulations apply to all patient testing performed on US patient specimens.

Currently because most of the genetic tests are considered high-complexity testing, laboratories providing these tests are subject to the general CLIA quality systems requirements for non-waived testing and the personnel qualification requirements for high-complexity testing.

For the specialty of clinical cytogenetics, there are also specific quality control requirements and the qualification requirements for the technical supervisors.

There are no specialty or subspecialty requirements for molecular or biochemical genetic testing because these tests are not considered a specialty or subspecialty under CLIA.

Besides CLIA regulations, FDA has regulations for IVD products. And for manufacturers, the FDA oversight is also enforced on certain laboratory developed tests such as the IVD MRAs.

Some state programs such as the New York State and Washington State Laboratory Programs and the deemed* status of accrediting organizations may have more specific standards for genetic testing laboratories. Also there are the professional practice guidelines and the voluntary standards developed by professional societies in standard-setting organizations.

In addition there are the good laboratory practices implemented by individual laboratories to comply with regulatory requirements and also to adhere with voluntary

standards. And this is the realm that we try to help with the CDC good laboratory practice guidelines.

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The two CDC guidelines that I am reporting today are based on the recommendations of the Clinical Laboratory Improvement Advisory Committee which is a federal advisory committee just like SACGHS.

CLIAC was established under the Public Health Service Act back in 1992. And CLIAC provides scientific and technical advice to the government regarding clinical laboratory standards including CLIA regulations and their impact on medical practice and laboratory practice. CLIAC also provides advice regarding the need to make modifications to existing CLIA requirements to accommodate advancing technologies.

CLIAC reports to the HHS Secretary and Assistant Secretary for Health, and the leading officials of the CDC, CMS, and FDA. It is managed by the CDC's Division of Laboratory Science and Standards which is where I work in CDC.

(Slide)

The need for improving quality assurance practice and oversight for genetic testing was recognized back in the late 1990s. In 1997 federal advisory committees started to work with advisory committees including CLIAC and other stakeholders to consider ways to improve the quality of

genetic tests.

In 2007 CMS developed the action plan to enhance the oversight for genetic testing by providing guidance rather than prescriptive regulations and by providing training to CMS and state CLIA surveyors by developing educational materials for genetic testing laboratories regarding CLIA compliance by collecting data on genetic testing quality issues and so collaboration of all stakeholders.

In 2008 SACGHS published the report, U.S. System of Oversight of Genetic Testing, which also supported these approaches.

In September 2008 CLIAC provided recommendations for good laboratory practices in molecular genetic testing and also recognized the need to develop a separate guidance document to address biochemical genetic testing.

In 2009 CDC published the *Morbidity and Mortality Weekly Report* publication that incorporated the CLIAC recommendations for molecular genetic testing.

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This is what the CDC MMWR guidelines for molecular genetic testing looks like. And this is a comprehensive document that includes discussions on the oversight issues and the quality assurance concerns recognized in molecular genetic testing as well as the process of how this guideline was developed.

The main body of this document provides recommended good laboratory practices to address the practice issues that had been recognized as needing clarifications for laboratories to comply with existing CLIA requirements and also to provide specific quality assurance guidance.

So the recommendations address the total testing process including the preanalytic, analytic, and postanalytic phases of molecular genetic testing. The recommendations also address the laboratory's responsibility regarding authorized persons particularly in situations when direct-to-consumer genetic testing is involved.

Also the recommendations address laboratory practice to ensure confidentiality, laboratory personnel qualifications and competency factors that should be considered before introducing new tests, and the quality management system approach in molecular genetic testing.

(Slide)

On the biochemical genetic testing front, in 2009 a CLIAC workgroup was formed and worked very hard to formulate input addressing good laboratory practices for biochemical genetic testing and newborn screening.

At the February 2010 CLIAC meeting, the committee provided recommendations for biochemical genetic testing and newborn screening that is performed for diagnosis and monitoring of inborn errors of metabolism.

So similar to the practice issues for molecular genetic testing, the CLIAC recommendations encompass issues including the total testing process, personnel qualifications and competency, the factors that should be considered before introducing new tests, confidentiality practices, and the potential benefit of implementing the quality management system approach in biochemical genetic testing and newborn screening.

I believe a copy of the full set of CLIAC recommendations is included in your binders. And for the audience you can download the full set of CLIAC recommendations from our division's website.

So currently, we in CDC are in the process of developing a new MMWR guideline to include these CLIAC recommended good laboratory practices.

(Slide)

I would like to highlight some of the recommended practices that will be included in the CDC MMWR guidelines.

So the MMWR document for molecular genetic testing addresses molecular genetic testing for heritable diseases and conditions as well as molecular genetic aspects of complex tests that encompass both molecular genetic test procedures and other test methods.

And the upcoming MMWR for biochemical genetic testing and newborn screening will address genetic testing for

screening, diagnosis and management of inborn errors of metabolism to include biochemical genetic testing. And this includes the diagnostic or confirmatory biochemical genetic testing performed for presumptive cases out of newborn screening and newborn screening for inborn errors of metabolism.

This document will also address the biochemical genetic aspects of complex tests that encompass both biochemical genetic test procedures and other test methods.

(Slide)

So the recommended practices for the preanalytic phase of biochemical molecular genetic testing as well as newborn screening encompass these practice issues. First of all, the information those laboratories should provide to users of their services. And users of laboratory services include healthcare providers, patients, payers and other individuals who may request a laboratory test and receive laboratory test results. In addition to that, the laboratories have responsibility for informed consent and laboratory practices pertaining to test requests, specimen submission, handling and referral as well as the practices for preanalytic system assessment.

(Slide)

I will go a little more in-depth on the first two issues. So as a general principle, laboratories should

provide information on the genetic tests they perform to users of their services. And this is to facilitate, first of all, the selection and request of appropriate genetic tests. And this is because currently genetic testing for most diseases and conditions is performed using laboratory developed tests. So without laboratories making the specific test information available to their users, it will be difficult for healthcare providers to access this information let alone to correctly use these genetic tests.

Also laboratories should provide information to facilitate appropriate collection, handling, transport, and submission of patient specimens in addition because many genetic tests require the laboratories receiving of patient specific information to start with and this may include the patient's race and ethnicity, family history, pedigree and other clinical information.

So it is recognized as good practice for laboratories to inform and communicate this need onto their test requesters so that by doing this, laboratories can facilitate their prompt initiation of patient testing and timely result reporting. Ultimately laboratories should be responsible for providing information that is necessary for informed decision making by the patients and their healthcare providers.

(Slide)

Here is a brief summary of the information that laboratories should provide for each molecular or biochemical genetic test they perform. So just rather quickly, this includes intended use, indications for testing, test methods to be used, the specific analytic performance specifications, clinical validity information and limitations of the test, whether the test is performed using a FDA approved or cleared test system, information to facilitate appropriate specimen collection, handling, transport and submission, and the types of patient information needed by the laboratory, the likelihood of test results to have implications for family members, availability of laboratory consultation, as well as cost information when ever possible.

We do see that this list covers a lot of information fields proposed for the Genetic Test Registry and I think it is helpful to point out that it is already recognized good laboratory practice that laboratories provide these pieces of information for the genetic tests they perform.

(Slide)

In terms of informed consent for molecular and biochemical genetic testing, laboratories should provide users with information necessary to make informed decisions and this includes the pieces of information that we just discussed, whether informed consent is required or not. It is recognized that unless mandated, obtaining informed consent generally is

not considered the job of the laboratory, however, when informed consent is required, laboratories are responsible for assisting healthcare providers in determining appropriate level of informed consent and also laboratories should provide appropriate means on test requisition forms to facilitate the documentation of informed consent.

For newborn screening, CLIAC recommendations are that explicit parental consent is not necessary for mandated public health newborn screening that meets the accepted criteria. For new tests that do not meet the accepted criteria, explicit parental consent should be required. Also parental and provider education should be integral to newborn screening programs regardless of consent requirements. And research use of test specimens should have appropriate human subjects protection procedures.

(Slide)

For the analytic testing phase the recommended practices address the establishment or verification of analytic performance specifications as well as documentation of available information on clinical validity. The molecular genetic testing MMWR provides specific guidance for quality control procedures in molecular genetic testing and the upcoming MMWR for biochemical genetic testing and newborn screening will address specific quality assurance issues in these areas of testing as well as other specific analytic

issues including reagents, standards and reference materials, equipment, software calibration, and calibration verification procedures.

Also laboratories should participate in available proficiency testing programs for each genetic test they perform and should follow the recommended practices for alternative performance assessment when PT programs are not available.

(Slide)

For the postanalytic phase, test reports overall should provide information necessary for accurate understanding and interpretation of test results by healthcare providers and other individuals who may use genetic test results.

The content must comply with the general CLIA requirements and should include the recommended additional information and I would like to refer you to the molecular genetic testing MMWR and the set of CLIAC recommendations for the details of the recommended additional information.

In terms of report retention, molecular genetic test reports should be retained as long as possible, at least for 25 years. And biochemical genetic testing reports that indicate genotypic information should be retained for at least 21 years.

The retention of newborn screening test reports is

subject to CLIA and applicable state requirements.

(Slide)

The retention of test records must also comply with CLIA and other applicable requirements. And in terms of tested specimens, for molecular genetic testing, the specimens that are stable should be retained as long as possible to meet the laboratory's needs to conduct quality assurance, quality improvement, and personnel competency assessment. These specimens should be retained at least until the next proficiency testing or alternative performance assessment to allow the opportunity to identify possible errors in patient testing and to take corrective action.

For biochemical genetic testing, specimens should be retained as long as possible, at least until after the final result reporting. And if possible, these specimens after completion of patient testing should also be retained until the next PT or alternative performance assessment.

The retention of newborn screening specimens is subject to applicable federal, state, and local requirements.

The recommended practices in the upcoming MMWR will also address postanalytic systems assessments for biochemical genetic testing and newborn screening.

(Slide)

In terms of personnel qualifications, laboratory directors must meet the CLIA qualification requirements for

high-complexity testing. Technical supervisors for molecular or biochemical genetic testing should have equivalent qualifications to CLIA requirements for clinical cytogenetics technical supervisors or have current certification in molecular or biochemical genetic testing by a board approved by HHS.

For public health newborn screening, technical supervisors must meet the CLIA qualification requirements for high-complexity testing and should have four years of training or experience in newborn screening. They also should meet any applicable additional state requirements.

Clinical consultants, general supervisors, and testing personnel must all meet applicable CLIA qualification requirements and should have training or experience that is relevant for the testing their laboratories perform.

(Slide)

The intended users of these good laboratory practice guidelines certainly include laboratories that perform molecular or biochemical genetic testing or newborn screening for inherited metabolic diseases.

We also expect that these documents provide a useful resource for these non-laboratory entities. For example, users of laboratory services, to improve their utilization of genetic testing services for health professionals such as laboratory surveyors and inspectors to help them with

evaluation of laboratory practices, for standard-setting organizations and professional societies when they develop new standards and guidelines for federal and state agencies, in consideration of genetic testing quality issues for IVD manufacturers when they develop new test systems, and also for the general public to help them have a better understanding of quality issues pertaining to genetic testing.

(Slide)

Currently we are working to provide information dissemination for the molecular genetic testing MMWR by developing audience-specific educational information for different stakeholders such as laboratories, healthcare professionals, patients, and consumers. Also by providing answers to frequently asked questions on our Division's website and by providing continuing education activity.

And for the upcoming MMWR for biochemical genetic testing and newborn screening, this is currently a collaborative effort of CDC with input from CMS and FDA. And we expect to be able to publish this new guideline in 2011.

(Slide)

We hope that these good laboratory practice guidelines will help to improve the quality of laboratory genetic testing services, to enhance the oversight for genetic testing under the current regulatory framework, and to improve the healthcare outcomes for patients who receive genetic

testing.

(Slide)

I have some resources here if you need information regarding the CLIAC recommendations on biochemical genetic testing and newborn screening and information regarding the molecular genetic testing MMWR, you can go to our Division's website that is on the right hand side of the screen. And for information on MMWR continuing education, it is available on the CDC's MMWR website.

(Slide)

The development of these CDC guidelines has been a huge effort and we would like to acknowledge CLIAC since 1997 as well as the CLIAC Molecular Genetic Testing Workgroup, the CLIAC Biochemical Genetic Testing Workgroup, and our CMS and FDA colleagues. And last but not least, we also need to acknowledge the CDC participants. I am delighted to see some of the participants in these efforts here in this room. Dr. Andrea Gonzalez and Dr. Vicky Pratt both participated in the CLIAC Molecular Genetic Testing Workgroup. And Dr. Liz Mansfield represented FDA on the CLIAC Molecular Genetic Testing Workgroup.

(Slide)

I have some questions and issues that we would really appreciate input from this committee. So before we go on to these questions, may I ask are there questions so far

for what I have presented?

Question and Answer Session

DR. TEUTSCH: We have limited time so let's just take a couple of questions here and then I suggest that you go through these but we may have to provide some input offline. So let me start with Liz since you were involved with this process and then Marc.

DR. MANSFIELD: Well I just wanted to kind of correct one little thing that Bin said for anybody whose blood pressure shot up when she said that FDA is regulating IVD MIAs; we are actually not doing that yet so that is not a subtle FDA way of announcing our intentions.

DR. CHEN: Thank you.

DR. WILLIAMS: So I am actually going to skip to the first bullet here and give you three specific areas that I think do need clarification.

In postanalytic phase, Number 2 in the key points, you state laboratory reports should be electronic or electronically compatible. In the informatics world, that would be defined as not adequately explicit. So what does that mean? A PDF paper file and an electronic health record would technically be compatible. There are huge issues relating to this, some of which have been discussed at this table and I am not going to go into great detail about this, relating to deficiencies in our current ability for electronic

information systems to represent genomic data and other types of data. And so I think if you are really serious about this, then there has to be a lot of attention paid to what exactly you really mean here.

Also in postanalytic, in clarifications 6(a) genetics consultation, you indicate that the CLIAC considers genetic consultation as encompassing genetic services and you specifically articulate genetic counseling services. Again as we have reported out of this committee in the access, there are significant issues relating to genetic counselor reimbursement. And I think if you really are encompassing this, and this is a recommendation to CMS, that this is really critically, then I think it is incumbent to address some of the issues about how we actually compensate genetic counselors particularly using the genetic counseling code that was created but was elected not to be covered by CMS.

And then lastly, the issues relating to personnel, and this has been a recurring problem and this may reflect some ignorance on my part, probably does reflect some ignorance on my part in terms of actually reading the CLIA requirements relating to these different categories, but over, and over and over again it talks about being an M.D. a D.O. or a D.P.M. which is interesting if you think about how a podiatrist would actually have any impact but they could run a laboratory, it looks like as I read this.

But under none of these areas are individuals with certification as Ph.D.s in biochemical and molecular genetics really articulated as being eligible to be a technical supervisor or a laboratory supervisor. In fact the only place that Ph.D.s are referenced, relates to clinical consultant qualifications which while we do have a handful of Ph.D.s that are providing clinical consultation, the vast majority of certified Ph.D.s in molecular and biochemical are in fact working in laboratory positions and many of them are the directors of those programs. I think that that is something that really needs to be clarified within these recommendations; and I don't know, Andrea may want to add more to that. That has been something that has also been talked about at this committee and I believe is also referenced in our Access Report from a few years ago.

DR. FERREIRA-GONZALEZ: I wasn't involved in the biochemical report but under CLIA you can be a Ph.D. actually and have some certification and be able to be a consultant, a technical director, a supervisor and so forth. So it needs to be reflected in that document. Thank you for pointing it out too.

DR. TEUTSCH: So Bin, do you want to go back to your last slide and let's see if there are any other specific thoughts about topic areas which we think CLIAC should be addressing in these areas and then about implementation of

these standards. Are there things here we need to share here with Bin?

DR. FERREIRA-GONZALEZ: I just want to recognize the amount of work that Bin Chen has been doing for the last two or three years to come out with these; a lot of people working together to come out with extremely valuable recommendations that will be extremely useful for everybody in the laboratory community so I want to thank you for that.

The second comment that I have Bin Chen, have you talked to anybody at the CAP Lab Program, the laboratory accreditation program, to see what are some of the most citations for these types of laboratories? See how they are addressed in the MMWR and maybe develop the frequently asked questions to those specific areas to provide more guidance. Instead of those that have already been identified, there might be some deficiency.

DR. CHEN: Well we are trying to reach out to standard-setting organizations and accrediting organizations to see how we can collaboratively promote the use of these MMWR recommendations. And I should say some of the MMWR recommendations were developed to address the deficiencies identified by CAP through their on-site laboratory inspections; for example, the lack of documentation on alternative performance assessments and other deficiencies. So it is our hope that by providing recommended good

laboratory practices specifically for those issues, we are not only helping accrediting organizations but also helping the laboratory community to develop improvements in these areas of laboratory practices.

DR. FERREIRA-GONZALEZ: The way that we have worked in the past in trying to educate laboratories about good laboratory practices has been through workshops at the annual meetings of different societies like an Early Bird or some other companion organization. So maybe you can line up with some of the professional societies that most of these directors are going to be attending and provide a workshop. You just need to get a room and you will be amazed at how many people will attend these sessions. And make it very interactive with those individuals. That will really bring all the biochemical and newborn screening directors to be able to learn more about this guidance.

DR. CHEN: Yes we have been doing that. We provided an Early Bird session at last year's Association for Molecular Pathology meeting and we also provided updates and presentations at the meetings of the American College of Medical Genetics and the APHL Newborn Screening and Genetic Symposium and other meetings. And we plan to continue to do that not only to promote the published molecular genetic testing document but also for the upcoming MMWR for biochemical genetic testing and newborn screening.

DR. TEUTSCH: Well thank you very much Bin. We really appreciate this important work and clearly it has been a topic that has occupied us in the oversight so it is great to see all the incredible amount of effort that it has taken to bring this to fruition and we look forward to seeing how this all gets implemented. I would encourage everybody, since we did not have a lot of time to discuss the issue, if you have additional comments and thoughts specifically on the questions that Bin raised, feel free to get them back to her directly. But thank you so much for joining us, we really appreciate it.

(Applause)

Public Comment Session

DR. TEUTSCH: At each of our meetings we set aside time for public comment and we both welcome and value the comments we receive as part of the public forum. So we move to that part of our program now. As always I will ask our presenters to stay to the five minute limit for their presentations but you should have in your folders their full written comments which will be made part of the record.

So let’s begin with Martin Naley who is Vice President of Cell Culture Research with Life Technologies. We appreciate you joining us today and we look forward to your comments.

Martin Naley

Life Technologies Incorporated

MR. NALEY: Okay, very good, thank you. My role at Life Technologies has changed. I am the Chief of Staff for Life Technologies. I have been in that role for about two years since the time that Invitrogen Corporation and Applied Biosystems came together into one large company providing research tools as well as tools for applied science and evermore useful in the world of health research and healthcare.

So if you are anything like me, you are getting pretty darn hungry so I will try to keep this quick for all of our benefit.

My remarks relate to this afternoon's session on implications of the affordable human genome and whole-genome sequencing. Last week I attended the American Society of Clinical Oncology Conference in Chicago. As you know, cancer is a disease of the DNA and the field of oncology already incorporates biomarker analysis into many of its clinical decisions.

At the conference, presentations on genomic analysis were extremely well attended. An example was a session held in the afternoon one day led by Tyler Jacks of MIT in which Jeff Trent spoke about some of the work that is happening at TGen. I can tell you that over 1,000 people were in that

room. There is a tremendous thirst in the medical community for the appropriate use of genomic information and people are interested and looking for ways to interact with these technologies.

Today's diagnostic tools are good but there is room to further improve upon them. Genomic technologies are moving from the research to the clinic and we believe that that transition is happening remarkably quickly.

This meeting about the implications of the affordable human genome could not happen at a more opportune and crucial moment.

What I will do, kind of deviating a little bit from the written remarks that you have in your binders, is cut straight to some considerations and suggestions that you might take in mind as a committee and then what I will do is back up and talk about some of the actions that are underway at Life Technologies and a little bit of the rationale for these recommendations.

So these suggestions, I have four here, first is to establish rapid biomarker review mechanisms to ensure responsiveness in incorporating biomarker knowledge into treatment decision rules. The second is a consideration of evaluation criteria for genomic technologies used in medicine. We recommend emphasis on the raw accuracy of sequence detection events; I will explain that in a moment. We also

encourage the continued facilitation of the development of information exchange networks incorporating genomic patient data. And these should ensure patient confidentiality and build upon other efforts to establish electronic health records nationally. It would be helpful to integrate genomics-based decision support rules in a broader health IT initiative. And fourth, investing in continuing education and training for health professionals and this includes genomic specialists as well as basic knowledge for frontline care providers.

So with that I will explain a little bit about what Life Technologies has been doing in the field of genomic medicine. We have been actively engaged in carefully designed evaluations aimed at brining whole-genome analysis to medical practice. Early this year we announced a small pilot trial through a partnership with US Oncology and the Translational Genomics Research Institute, TGen, to use whole-genome sequencing to find novel, previously unconsidered treatment options for 15 triple-negative breast cancer patients. Through that work we are developing supercomputing infrastructure to analyze human genomes and to elucidate treatment options. We hope to make a difference in those patient's lives as we do so.

Last week at a conference in Boston we announced the Genomic Cancer Care Alliance, a project that builds on the

capabilities of the triple-negative breast cancer trial. This Alliance of eight entities will evaluate the use of whole-genome sequencing as a method to find treatment options for cancer patients across tumor types who have failed to respond to first line therapy. The study will use whole-genome sequence and transcriptional analysis of patient's tumor and normal tissues followed by rigorous bioinformatic and clinical analysis. A dedicated tumor board will meet to discuss every patient, developing treatment plans that are tailored to the individual's biology. We will collect data to assess clinical utility and economic impact.

That study targeting 100 patients will begin enrolling patients later this year. Life Technologies is the primary funding sponsor for that work and our partners are Fox Chase Cancer Center, Scripts Health, El Camino Hospital, TGen, US Oncology, and a major university CLIA lab as well as Omicia a bioinformatics and interpretation company.

Our second expectation as we look out in the field here, is that genomic inquiry may prove more powerful than targeted diagnostic tests in certain instances. And instead of limiting testing to already well described pathways, clinicians are allowing the genome to speak and are open to treatment options based on what they find in this open inquiry whole-genome profiling.

The findings may suggest the use of drugs that are

currently approved for different indications than a patient is presenting with. For example, a testicular cancer drug may be selected for a patient with brain cancer due to the underlying biology of their cancer. For complex tumors with multiple mutations, a combination therapy approach may be recommended to restore proper cellular function. And these treatments may be different from the decision rules that are currently in place.

Just to work within my five minutes I will pass some other stuff here.

To ensure that biomarker findings at the individual patient level are consistently measured and comparable, standards may be needed for technologies used in whole-genome sequencing. And it is essential that users of the technology be able to discern true genetic variants from test artifacts.

To that end, as the FDA potentially explores quality criteria for this sort of instrumentation, it is imperative to consider raw data accuracy. This may be a new term for some people in the audience so I will explain it and I would like to introduce this into the lexicon.

So there are two measures of accuracy in whole-genome sequencing. One is the accuracy of the raw data coming from a sequencing detection event, at the actual biochemical level. The other is the accuracy of the data after analysis which can be considered processed data accuracy. We believe

that raw accuracy is the ultimate driver of quality and cost for genetic information. And with high raw accuracy sequencing, coverage is more about seeing deeply into the biology not about compensating for error rates.

Another element is facilitating data exchange standards perhaps creating a centralized information exchange for relational data between mutations, biological pathways, drug mechanisms of action, and clinical outcomes.

And as a thought on this, as diseases become evermore specifically stratified, patients with similar biology may be further and further apart from one another. When you think about that, you may need to be able to compare patients who are across different medical systems. And I think this introduces a new rationale and a different need for interoperability. It is more than when a patient moves, it is about being able to see and stratify disease across a very broad population.

And the medical education part we have discussed before so I will leave that.

So we believe that whole-genome sequencing is compatible with the other programs in the Healthcare Reform Act earlier this year around cost savings. We believe that this will not be a net cost add and that it will lead to more specific treatment decisions for patients, for better health outcomes, and better cost.

And there is much work to be done. HHS has a major role to play to ensure that genomic medicine is available to benefit patients and society as quickly as possible. So thanks for your consideration. I am here for the next two days and I would be really happy to talk with any of you.

DR. TEUTSCH: Great, we have time for one or two comments.

(No response)

DR. TEUTSCH: Good, well thank you so much, we appreciate it and we will take that into consideration as we listen to all the discussions this afternoon. Is Klaus Schafer here? He had signed up.

All right then let me move on to Mark Sobel who we again welcome back from the Association for Molecular pathology, we always appreciate your input.

Mark Sobel, M.D., Ph.D.

Association for Molecular Pathology

DR. SOBEL: Good morning. AMP commends the SACGHS for focusing on whole-genome sequencing, an area of growing interest in the Association. Sequencing technology is advancing at a rapid pace with not only the cost and turn-around time of processing a single sample dramatically decreasing but also the idea of sequencing an individual's entire genome moving from feasibility to reality.

In time as costs and turn-around times decrease

further, whole-genome sequencing technology will make targeted molecular tests less cost effective. It is reasonable to foresee whole-genome sequencing techniques in a clinical laboratory and by extension the clinic in the next five years and as such AMP commends the committee for investing time to explore and address the related challenges of policy and practice issues.

As the technology advances, AMP's concerns focus on the clinical applications of whole-genome sequencing. The advent or adoption of the technology itself is not controversial but how clinical laboratories apply the technology and physicians utilize the information to inform clinical decision making can generate many ethical challenges and laboratory practice questions.

On a broad level, currently marketed molecular diagnostic tests encounter reimbursement and coverage hurdles. The current state-of-the-art may consider whole-genome sequencing as a screening test, placing it into a category with additional obstacles to adequate coverage and reimbursement by public and private payers. As all testing technology advances, AMP believes that reimbursement policies should be modernized to appropriately represent the value of the information obtained from the laboratory tests that utilize whole-genome analysis or next genome sequencing technologies.

The wealth of data obtained in whole-genome sequencing creates new practice questions that molecular pathologists will have to address. AMP believes that the cornerstone of integrating this technology into laboratory practice will be the assessment of its clinical utility. How can 3 billion base pairs of sequence and identification of the sequence of around 20,000 genes be coupled to clinical utility? The answer to this rhetorical question is that there will be difficulty for molecular pathologists to associate meaning with the data generated by these tests and there will be further challenges to define a normal genome.

An effective approach to the central question will depend upon a multi-disciplinary research agenda which is critical to enabling accurate diagnostic interpretations. Also there should be a central repository to submit clinical and analytical data of these analyses to further inform the interpretation and clinical utility of results.

Moreover, the vast amounts of data will require investments in bioinformatics technology not only to analyze, manage and store the data but also to enable secure access to the data in a useful manner. Measures to standardize the data for entry into interoperable electronic medical records and to simplify the reporting of sequencing results will be required to ensure responsible adoption and implementation of this technology.

When healthcare provides request whole-genome sequencing for a patient, they may indicate or describe a phenotype and/or symptoms. AMP is concerned that this poses an ethical quandary when molecular pathologists have access to the entire genome dataset but the provider is only interested in the interpretation for a specific indication. AMP members question whether it is responsible and appropriate to only report based on the test indication or whether there is a duty to report all findings regardless of the initial clinical indications for the test. In these instances, AMP members will need to consider whether they should mask the non-relevant data and only report based on the test requisition. Additionally they will consider whether to then report data as new evidence as additional gene disease associations become available. AMP encourages the committee to consider the complicated ethical issues associated with the duty to report all data, interpretation as new evidence emerges, and the appropriateness of masking data irrelevant to the test prescriber's indication.

AMP has provided comments to the committee in the past on the issue of DNA patents and has been pleased with the committees report and recommendations on this business practice. As whole-genome sequencing becomes more widely used in the clinical setting, DNA patents on specific sequences may restrict the reporting and interpreting of the full results of

such testing. This links to our concerns about clinical utility and the duty to report all results. And AMP fears laboratories performing whole-genome sequencing may face infringement liability or risk incomplete reporting of clinically significant data.

Confounding these ethical issues are the anticipated communication gaps among the laboratories, physicians, and patients. Molecular pathologists will have the added responsibility of educating the healthcare providers who request whole-genome sequencing about the complexities of genetic associations, risk information, and laboratory decisions about which data to report and in what manner.

These healthcare providers will in turn have the challenge of communicating the significance of this information to patients. With other areas of genomic medicine, AMP has recommended that the committee continue to explore the provider education and training needs associated with implementing whole-genome sequencing techniques into the clinical setting. AMP is aware that the committee has released its draft report on the education and training of healthcare professions and we intend to submit comments later this month.

AMP wishes to clarify that next-generation sequencing techniques used in laboratory developed tests or in a test submitted to the FDA for approval for the purpose of

interrogating a specific gene or condition should not be viewed as whole-genome methods even though the same technology approach is used. A specific application using next-generation sequencing technology versus whole-genome sequencing is simply another laboratory test using evolving technology but used in a targeted manner and subject to the same appropriate validation as any other molecular diagnostic test.

Lastly, AMP values the role of whole-genome sequencing in characterizing the full genome of tumor samples. AMP members recognize that to truly capture the genomic changes associated with cancer, the results must be compared and contrasted with the patient's germline from normal tissue perhaps adjacent to the tumor or from a blood sample.

Similar to our previous concerns, molecular pathologists will have the responsibility of determining what, if any, information about the patient's germline genome should be shared with the patient. The committee and the sequencing community will need to address the ethical challenges associated with reporting large datasets before the technology is disseminated widely in the clinical setting contributing to the promise of individualized disease prevention, detection, subtyping, prognostication, treatment, and monitoring.

AMP thanks the committee for focusing its attention on whole-genome sequencing and looks forward to partnering

with the committee to explore these challenges that we have outlined today. To that end AMP has formed a working group on whole-genome analysis. Thank you.

DR. TEUTSCH: Thank you very much. We will be talking about I think a variety of those issues over the span of the rest of the day. Are there any comments or queries for Dr. Sobel?

(No response)

DR. TEUTSCH: Thanks so much. Hopefully you will be joining us for the discussion. Let me ask one more time, is Dr. Schafer here?

(No response)

DR. TEUTSCH: Are there any others who had something they wanted to say as part of the public comments? Marc, do you want to make a public comment?

Marc Williams, M.D., FAAP, FACMG

SACGHS Member

DR. WILLIAMS: Yes, this is actually reflecting back on our task to come up with something that comparative effectiveness assures by tomorrow. There was a very provocative article by Dr. Angrist behind Tab 6 that called for phenotyping and I had actually added that to my list of things to talk about as potential things that could be added to our CER Christmas list.

I would like to just put for your consideration,

Mr. Chair and the committee as a whole, whether or not a comment regarding an investment in a feasibility of collecting phenotype data in a standardized way would be something that would be worthwhile to propose to the Secretary from the committee. So I apologize that I had neglected to mention that before but I think this is a very powerful and cogent article and I think there could be an opportunity here.

DR. TEUTSCH: For those of you who have had a chance to read that, where there any thoughts about that?

(No response)

DR. TEUTSCH: Marc, I suspect we need to hear more just to understand what the implications are and what we actually would want to say. Do you want to formulate that tonight and maybe bring us back something in the morning?

(Laughter)

DR. WILLIAMS: Absolutely.

DR. TEUTSCH: And those of us who did not have a chance to read the whole thing will hopefully have a chance to look through that as you said in Tab 6.

Rochelle let me ask you one thing. We had some comments from Kathy this morning regarding the ACLU case and I did not know if there was -- because we had worked so long and hard on patents and you have been so close to this, I did not know if you had some additional thoughts you wanted to share before we break for lunch.

MS. DREYFUSS: Yes if you do not mind. It will take me a couple more minutes and it is a good follow-up on the representative from AMP because AMP is the named plaintiff in this case that was just decided by the District Court in New York.

Now Kathy mentioned that the case concerned product patents and process patents and the validity of both of those. One thing that I was uneasy about her presentation was that she acted as though the court was behaving in some way improper by not citing past cases about gene patents. In fact courts do not talk about cases that are irrelevant to the question that they have been asked and all of the past gene patent cases have been on issues like what kind of utility do you have to get a patent, how inventive the invention has to be to get a patent, none of them have asked the questions that are in the AMP case about whether this is patentable subject matter. So there really was not very much for the court to cite.

The Supreme Court case on this, Diamond against Chakrabarty is on man-made microorganisms and so Judge Sweet properly went back to the early cases about isolated naturally occurring substances and the case that he found was the case called Parke-Davis against Mulford which was also decided by his very own court, the District Court in the Southern District of New York in 1911. That was a case about

adrenaline and that has since been looked at by other courts which Judge Sweet also cited there decisions. And in those cases the issue about whether a naturally occurring substance is ever patentable is whether the naturally occurring substance is different in kind when it is isolated from when it occurs in nature. And Judge Sweet found that that is not true of DNA at least in the diagnostic application because what you care about is what DNA actually looks like in nature, not something that is different from nature. So as far as diagnostics were concerned, he did not think that gene products were patentable.

And then on the question of simple associations, the association between the BRCA mutation and breast cancer, he said that depended on the decision in Bilski which is currently pending before the Supreme Court. It is now the oldest case pending before the Supreme Court.

Now I did agree with Kathy that the chances that the Federal Circuit will affirm this decision are miniscule. They are a very pro-patent court and you can almost hear them writing their decision reversing that case as we speak.

But two points about that, first there is one other issue in the case which Judge Sweet dismissed because he found that under patent law these things were not patentable.

The third issue is a First Amendment issue, free expression, which I guess has its own application in the

genetics context. But the argument is that the ability to communicate with your doctor is inhibited if these genes are patented. As I said, Judge Sweet did not decide that issue because he dismissed the case on the grounds that these patents were invalid. Were the Federal Circuit to reverse on that, then this issue would then come before the court and I don't know what either Judge Sweet or the Federal Circuit would say about that. I think most people think it is a petty unlikely claim to win.

I also agree with Kathy that the District Court was really writing for the Supreme Court's attention and the question is whether the Supreme Court would take the case.

For the Supreme Court there is yet a fourth issue in the case and that is standing. You cannot just bring any case to court because you feel like it. You can only come to court if there is a direct injury to you personally. And it is not exactly clear that the plaintiffs that were brought before the District Court have standing to bring the case.

So if the Supreme Court were to look at it, they might just decide not to take it. They seem to be having a lot of trouble with Bilski so they might not take it at all or they might decide to vacate on standing grounds in which case it would be as if the whole thing had never happened. So that is where we are.

DR. TEUTSCH: Right, well thanks for that update and

we are going to continue to follow that with interest. A couple of things before we break, one I want to acknowledge David Dale is on the phone so we appreciate your being here with us.

(Dinner logistics discussed)

DR. TEUTSCH: Great, that was an interesting session and we will take a break for an hour and be back at 1:00.

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. TEUTSCH: So welcome back. This afternoon is really dedicated to the policy issues that surround the anticipated development of the affordable whole-genome sequencing. Our colleagues, Charis Eng and Paul Billings, have busily been working to assemble really a terrific set of speakers except for the last one --

(Laughter)

DR. TEUTSCH: Where they were desperate. But on the subject of the affordable genome which is really an exciting development and raises a host of opportunities, challenges, and issues some of which we began to hear about in the public comments earlier.

So with a reminder that a lot of the materials are in Tab 6, I am going to turn it over to Charis and Paul to lead this afternoon's discussion so thanks to you both.

Implications of Affordable Whole-Genome Sequencing

Moderated by Paul Billings, M.D., Ph.D. and Charis Eng. M.D., Ph.D.

The Affordable Genome

By Paul Billings, M.D., Ph.D.

DR. BILLINGS: So thank you to the committee for the opportunity to organize on this work and I want to thank Steve, Sarah, Kathy, and Charis and I am sure many others for the opportunity so far.

(Slide)

Since brevity is the soul of wit, I will try to fool you that I am going to be witty for the rest of my time on this committee by not saying very much right now. But I will say that many great geneticists have had a familiar motivation underlying their commitment to the field. Some of the founders of the field escaped the eugenics of World War II, other had troubling family histories. Victor McCusick was a twin. Some of you do not know it but I am a triplet, part of a triplet prior to the IVF era. One of my other two siblings is my co-chair on this committee, the distinguished Professor Eng.

(Laughter)

DR. BILLINGS: She is known around my family as Billings the Smarter. I relish this time working with her.

(Slide)

The other of the triplets lives here in D.C. on Pennsylvania Avenue in a big White House. Now you can recognize him as my twin by his good choice in ties and I can only just say that I too along with Sean Hannity and Rush Limbaugh have been looking for that birth certificate since last year because I hope it will allow me to share more ties with my brother.

(Slide)

There have been waves of popularity that have

afflicted the field of human genetics. Eugenics, of course, and the early eugenicist knew how to get to people, right. They appealed to the social part of them; I would have never gotten married if I had to produce my certificate.

(Slide)

Wrapped it in sex of course.

(Slide)

And then the early interest in public health issues and the broad interest within the community in those things.

(Slide)

Later eras of popularity included the integration of genetics into the medical mainstream.

(Slide)

And then of course the Human Genome Project which commanded great headlines and of course produced Kings.

(Slide)

We have now entered I guess the era of whole-genome sequencing with billboards; this being the most popular genetics-related billboard ever produced.

(Slide)

And this one which could be Craig Venter's new announcement, but actually was on the tabloid.

(Laughter)

DR. BILLINGS: Now there has been a dearth of hard facts, proven clinically, and many false starts and excessive

hype in human genetics. Now with due respect to Lee Hood and his concepts of systems biology and 4P medicine, the 4Ps I think are most -- are Practically unproven, Probably wrong and oversold, Potentially dangerous and wasteful, and Personally useless.

I would hope that as we evaluate all this information, we could reinstate the high ground and try to show humility, understatement, discretion and respect.

(Slide)

Now for me the core issue in this affordable genome charge resides in the paradox that has afflicted us for hundreds of years. While it is certainly true that the White House never saw a greater brain than those evenings when the great man Thomas Jefferson dined alone, he was no human geneticist and obviously did not learn much from his plantation work, animal husbandry, or consorting with slaves. Our results for over a century, and now more than ever, show that all men, in fact all people, are NOT created equal.

A major impact of the whole-genome sequencing will be, I predict, to irrevocably prove that and hopefully identify differences that are meaningful for individuals living in this great freedom-loving, entrepreneurial, welcoming society and country.

The tension between the results of affordable genomes and how they will be used for the benefit and not harm

of the individual from conception through death are the core themes and challenges that drive me and hopefully us who are gathered here today.

We may adopt policies and visions of this or write provisions in a report that are not necessarily the logical result of the data that we consider. We have done this before in my estimation. Why, because they serve the principles of this great country and are the right thing to do.

(Slide)

For me GINA and the state legislation that preceded it for two decades are examples of that. Making the advances that will surely result from full-genome knowledge and the personalization of medicine available to all who need and want it is another great cause. Affordability of good and hopeful technology which really means the availability of great, new, and insightful methods for proper care is as close to a non-enumerated right in this country as any I know.

Let me close by saying, asking Jefferson or Lincoln who probably had a connective tissue disorder, or our great paralyzed warrior president FDR, or all those presidents who gained ambition and energy from psychologically-linked variance, what their genomes tell us. There is no gene to be found by any means for wisdom or disability or potential for success in our world, in our genomes, or by whole-genome sequencing. But there may be clues to better treatment to

prevent suffering, to higher quality healthcare, and happier lives for some. There certainly is great promise and hope in what we will hear today for enlightening and moving a sub-culture in our country now dominated by graying traditions, sometimes stifling and costly regulations, and a moral obligation to first do no harm.

Our charge must be to critically analyze the notion of whole-genome sequencing for all; energize what it is or could be, and capture what is needed to make it a benefit to us, our families, and all our neighbors. Thank you and I am really pleased to be part of this.

Whole-Genome Sequencing -- Implications for Clinical Care

by Charis Eng, M.D., Ph.D.

DR. ENG: Well good afternoon. My twin and I are very pleased to be here but the triplet is sitting in the big White House.

(Slide)

My twin has set the tone for a great sense of humor so I would like to give a little bit of philosophy. Even in 2006, in genetic terms that is eons ago, Elias Zerhouni actually saw all of this and said personalized medicine, genomic medicine, is the basis to health and medicine transformation so we want to intervene before symptoms appear but how do we know who and what symptoms and what to do? So this is -- let’s have a great way to make preventive

diagnoses. To prevent, we have to detect patients at risk and this would be many orders of magnitude much more effective.

(Slide)

In 2009 PWC released its top ten health industry issues and you will see that genetics figures prominently. So genetic testing is reaching the price point for the masses. And some of the discussions this morning alluded to that and all its fallout. Technology is a powerful health extender.

(Slide)

Then in 2010, PWC released a whole bunch of stuff and if you read through it, and I will not do that, everything there is germane to this session on whole-genome sequencing. I just want to point out the last two, technology backbone and labor shortages. In fact, do you know that there are more astronauts in this country than there are geneticists? That is a problem.

DR. : And they have more fun.

DR. ENG: They have much more fun.

(Laughter)

DR. WILLIAMS: It also explains why there is an ICD-9 code for weightlessness.

DR. ENG: And in the old days, in 1935, you know that there is an ICD code that says visitation by an angel, yes. And Emily Edelman can attest to that. I did not make it up.

(Slide)

Now, so today as the speakers speak, what are the gaps that have to be fulfilled from genomics content to clinical context; lots of scientific issues which you will hear, organizational, not even as many as astronauts, oh dear, and of course individual and societal needs.

(Slide)

So this is what I call my slide that ends happily ever after. So on the right is Nirvana otherwise known as the swan and you will understand why.

So when we talked to the speakers they said "should we talk about in ten years when we know everything, we integrate genetics, family history and genomics, we know everything that is actionable and we can fix it." And I said "well no, then there is nothing to talk about you just do it." We are somewhere in between this. We are in the ugly duckling stage. And so we have asked some speakers to address their expertise. And in fact some of the comments we heard in the public comment section are in the ugly duckling stage that will occur in the next year or two.

(Slide)

Now a few logistics; you know this harkens back to my twin's first slide. Be on time. So Kathy is sitting up here and she is going to hold up two minutes, one minute, and then you are out. And if that does not work, my twin and I

will begin to jump up in our seats. Well if you ignore us, then our Chair will come and get you.

(Laughter)

DR. ENG: In other words, “Brevity is the Soul of Wit, Therefore Thou Shalt be Brief” -- oops and I made a typo so double apologies to Shakespeare.

And before my poem I think we also -- Kathy wanted to say we will allow one or two burning questions after each speaker but they have to be clarifying. So without that clarification, the next* speaker will make no sense but otherwise hold your discussion until the end.

(Slide)

So now to end with a poem that will set the stage. All of you I dare say are familiar with the first stanza but not the next one. “Still, thou art blest, compar’d wi’ me The present only toucheth thee; But Och! I backward cast my e’e, On prospects dear! An’ forward, tho’ I canna see, I guess an’ fear!” And on that philosophical note, I will turn this over to my twin who will introduce Dietrich.

DR. BILLINGS: Thank you. So the first speaker is Dietrich Stephan who is the Founder and President and Chief Executive Officer of the Ignite Institute for Individualized Medicine which is an enormously important industrial-sized translational genomics house.

Dietrich has worked tirelessly on common human

diseases and founded a number of important companies including Navigenics, Amnestix and with some other very important people Aueon and Company. Prior to this work and prior to the border and undocumented people legislation in Arizona, Dietrich was a senior member of TGen and later on moved to be the Deputy Director of that institute. He is going to tell us today about whole-genome sequencing.

Overview of WGS

by Dietrich Stephan, Ph.D.

DR. STEPHAN: Thanks Paul and thanks Charis for the invitation to be here today. I have been tasked with giving you a brief introduction of next-generation sequencing given that I think we can all anticipate that it is going to be feasible to get a reasonably inexpensive and reasonably accurate sequence and set the stage for the following speakers.

(Slide)

So what I would like to cover is why would you want to sequence a full genome first of all? And there are really two applications; one is in the research space and one is in the clinical space and I will try and give you a couple of teasers as to why we would want to do that simply so you can frame the content you will be getting over the next three or four talks.

I have also been asked to give you some key

definitions surrounding whole-genome sequencing so that as we hear about platform technologies and different nuances that will impact the implementation of those in both the research and clinical setting, you can have a sort of understanding of that vocabulary.

I wanted to also give you a sense of the trajectory of the technology. As we all recognize, the field is moving very quickly but perhaps more quickly than we would anticipate or in some cases than we would like.

How do we extract maximal value from the technologies, and I will touch briefly on how you partition or suck out regions of the genome of interest so you can specifically sequence those and why you would want to do that.

And then just touch on, again just sort of in the vein of nomenclature, but when we talk about second-generation or third-generation sequencing, what types of technologies are we talking about and what are the different applications and issues around those?

And finally I am not going to talk a lot about assembly analysis and interpretation of the genome in either the research or clinical setting but clearly this is the nut that I think this oversight body needs to grapple with as we turn on these very powerful technologies. And I will just leave it there as well.

(Slide)

So why would we want to sequence a full genome? Specifically in the research setting there is incredible value given that all human disease except maybe trauma has a genetic component and articulation of that heritability around both monogenic single gene disorders and common chronic complex genetic disorders has value. So what is that value?

The value comes in terms of being able to predict what your heritable component or risk is either pre-symptomatically or for use in achieving a better differential diagnosis; so on the diagnostic side roughly. And then on a therapeutic side, so really understanding the core pathogenesis or the core biological networks undergirding all of these diseases is the core of developing knowledge-based very highly-targeted therapeutics.

So what are we going to be doing with the technologies that are coming online and I will talk to you about how they are going to reach a price point where we can start to really see them flare-up in the research space. We are talking about in the early part of next year having the ability to sequence, at volume reagent cost, a genome at about $3,000. What can that power in terms of research studies?

Well we have this huge backlog of case-control cohorts, clinical samples that have been very well characterized around diseases that we all want to solve; Alzheimer’s disease, autism, cancers, cardiovascular disease,

neurological diseases. What we can do is take lots of individuals with those diseases versus lots of individuals without those diseases and simply sequence through the entire genome and extract that missing heritability that lets us get insight into those diseases.

This is something that we could not do before with for example genotyping technologies, whole-genome association studies, so we will be able to find not only the common variants that are floating around in the population and inherited across generations but those more rare variants that predispose to disease as well as the modifications of the genome. All of these technologies that we are talking about today, second-, third-, fourth-generation sequencing technologies can articulate epigenetic variation of the human genome and they can also identify copy number variants. So those four classes of variants basically comprise the vast majority of heritability for human diseases.

What we can also do, and that is just understanding what is different between people with and without disease, is what we can also do is understand the variation within individuals with diseases.

So we all know that, for example, Autism Spectrum Disorder is an umbrella diagnosis and there exists incredible clinical heterogeneity across that diagnosis where on one end of the spectrum we have kids with Asperger's that are very

high functioning. On the other hand we have kids that have classically been labeled with mental retardation. We have nuances within that umbrella diagnosis and so these technologies that we will be talking about today have the ability to tease out specific subclasses of those diseases which will then form the basis of a new molecular nomenclature. So autism sub-types 1 through N and the foundation for a new wave of exposure epidemiology and drug development. So that is essentially what we loosely call personalized medicine right now but these technologies will power that sub-classification.

(Slide)

On the diagnostic side in terms of articulating heritable risk, I think we have all become familiar with the strategies around this over the last couple of years with companies like Navigenics and 23andMe and deCODEme where really you try to, and within an entire population of individuals which you see on the upper left hand side of the slide, understand which of those individuals has a higher germline risk for specific mutations. And this is still largely in the research space.

But for example, how can you classify across a population individuals that have the highest heritable risk for a common disease and treat those individuals differently across their lifetimes? This is still largely evolving in the

research space but there needs to be research around how would you take this 5 percent of people with the highest heritable risk for this disease, tell them strategically how to avoid exposures, tell them strategically how to stratify their screening behavior, diagnose them earlier, and what drugs they might uniquely respond to. This is one application, I think, of whole-genome sequencing that is going to become very robust; so diagnostics loosely said.

(Slide)

On the therapeutics side, we have seen that genome scanning technologies and sequence technologies have the incredible ability to pop out biological circuits that form the basis of robust drug discovery. So on the research side, whole-genome sequencing can give you better and more accurate insight into the biological circuits that drive diseases so that you can aim drugs at them more specifically and very quickly move into preclinical models and then humans for specifically these common diseases.

(Slide)

This is a teaser also of the future to come. But you can also start to aggregate all of this type of molecular data and do even better drug development. This is a group formed by Stephen Friend and Lee Harwell and others around really using the human genome either as an aggregate or from an individual to perturb steady-state somatic networks with

the output being highly accurate drug development.

(Slide)

And this is just an example, and again you can envision a day, and I am sure maybe in five or ten years this group will be asked to look at this, what happens when you take an individual's genome and all the variants in that person's genome, bang it up against that network in the sky that is the steady-state network of how the human body behaves, and get an output of what drugs that individual might respond to specifically and uniquely without any precedent and how do you regulate this type of activity specifically in the cancer space. I mean this is closer actually -- and here is some information about this today, how you use somatic variants, the cancer genome, to stratify the standards of care today and develop experimental or off-label therapies for that individual patient so that they can have an improved outcome. It is not as far off as we think.

(Slide)

There is a lot of exciting stuff in the research space but I think mostly what we would like -- and I think as a group we recognize that and are comfortable with the fact that these tools have incredible value in driving at new ways to diagnose and treat disease.

I think where we start to get concerned as a group is how do we, in the face of declining costs for a human

genome sequence, improving accuracy and an incredible body of information out there in the world that can be applied to a human genome sequence, how do we in a very short timeframe become comfortable with delivering that type of information.

So in 2001 we got the first human genome sequenced for $3 billion roughly. Today Illumina announced, Jay Flatley announced last week in Boston, that we can deliver a CLIA-certified human genome sequence for about $10,000. It starts to get within the realm of possibility for patients and physicians to order this.

And we have been doing fancy molecular genetic research against human diseases for the last ten or twenty years and that information is aggregated and has largely reached sort of a wall in the research space. Now it is a matter of applying this information to this genome at minimal cost, effectively, accurately, and safely.

(Slide)

So what value would we create for a person if we were able to do that? Let's say I could sequence your genome today for $10,000 and in a year it is $3,000, and two years from today it is $100 to $500? How would you use that?

And this is just an introductory teaser but you can imagine, for example, using a genome sequence to supplant metabolic screening when a baby is born. You could imagine using that heritable risk information to give risk

stratification information to people who are young but pre-symptomatic so they can manage their health portfolio effectively across their lifetimes.

You could imagine also using that information to stratify disease screening paradigms. So we have heard a lot of debate around women and mammography recently where the average age is -- you know the age where you get reimbursed is 50. What about those couple of percent of women who happen to be in the extremely high-risk category that do not carry a BRCA1 or BRCA2 mutation? How do we stratify their screening behavior better to improve outcomes for that subgroup?

And then finally when a person presents with their disease, how do we use the genome, the germline genome, to give them the right dose of the right drug to improve outcomes and reduce waste in healthcare?

So this is my attempt at just loosely saying the genome has value in a medical setting and we need to understand how to use it.

There is another application, there are loosely two applications, one is the germline genome, the genome you have been born with that does not change across your lifetime. The second is the cancer genome. We all know that cancer is a disease of a single cell and that cell's genome actually changes and it forces that cancer cell to continue to replicate unchecked. We can sequence the cancer genome, and

you will hear something wonderful from a group called the Cancer Care Alliance about doing that at the point of diagnosis or diagnostic biopsy. So pulling that cell out, sequencing it, and understanding how it will respond to drugs moving forward. And so there is a series of applications around cancer genome sequencing and stratifying care that I think will be incredibly important.

So when is all of this -- I like to call this convergence, the point at which the genome becomes accurate and cheap and we can start thinking about using it in a clinical setting. We have sort of seen the beginnings of this whole phase recently with the direct-to-consumer wave. Certainly in the monogenic space we have been doing it piecemeal. But I believe convergence will happen in a very short timeframe. You will see cost and accuracy hit a sweet spot within two years where we can really start to turn this on en masse in the clinical setting and we really need to figure out what to do with it quickly.

(Slide)

We talked about cancer sequencing. The way you -- if you get diagnosed with cancer, you go in to see your oncologist. They figure out it is either lung cancer or colon cancer or breast cancer and they turn to that page in the NCCN Guidelines and basically pick the first drug on the list and give it to you. If you fail that, they pick the second drug

on the list. If you fail that, they pick the third drug on the list. This is a paradigm that is starting to change with molecularly targeted drugs but largely this is the way it works.

What we can do, and I think you will see activity start here, again be able to stratify -- not change the standards of care, but stratify the standards of care. So say this individual, because they carry a BRAF mutation or a hypermetabolizer, should be on this drug at this dose as opposed to this one which they will not respond to and go through this decision heuristic in a better way so that they achieve maximal outcomes.

So those are some teasers; so research applications, clinical applications. On the clinical side you will see them loosely bucketed into diagnostics and therapeutics and the field is moving very quickly. How quickly?

(Slide)

Until recently, until just actually the middle of the last decade, sequencing was done on a gene-by-gene basis, it was very expensive, hundreds to thousands of dollars for a single gene and we have recently hit a technology evolution that has allowed that to increase exponentially.

This is sort of the point at which second-generation sequencing technologies hit and I will describe what those look like. We are on the verge of having third-generation

technologies hit which will drive us to this price point here and then the fourth-generations which will improve accuracy are probably two years away. But the technology is evolving faster than Moore's Law.

(Slide)

What are those technologies? So loosely, first-generation technologies are Sanger sequencing. They have a strand of DNA and you incorporate a fluorescent base and you read it. And these are highly accurate. They are the gold-standard for diagnostic platforms but they are largely unaffordable if you are thinking about a whole genome context. Think about Myriad and BRCA1/2 sequencing. Those are extremely expensive single gene sequencing tests.

The second-generation technologies are ones that are currently in use in the research setting and are stable and commercially available. Those loosely break down into the Applied Biosystems/Life Technologies SOLiD4 platform, the Complete Genomics platform which we will hear about today, the Illumina HiSeq platform, the 454 and the Polonator. These are really characterized by the ability to do those extension reactions in parallel and I will show you some of those slides describing that but these are becoming affordable. I talked to you about price points for a genome of around $10,000 for second-generation technology. They are reasonably accurate for research purposes but they are not yet accurate for

clinical purposes.

Third-generation technologies, these are single molecule sequencing technologies. The nomenclature here might shift a little bit between talks; some call these sort of 2.5 generation technologies. These are technologies where you literally are looking at a single molecule of DNA and measuring bases that are added on to it using fluorescence.

Fourth-generation technologies largely do not use fluorescence; that is the difference. Here these are solid-state technologies that can really look at native incorporation of bases and these can go much faster and have the potential for much longer read lengths and I will talk about that in a second.

But third- and fourth-generation technologies have the promise, these are not commercially available yet except for one platform, they have the promise to be very affordable for a genome but they are largely unproven; we do not know what the accuracy is yet.

(Slide)

A couple of definitions; I am sure all of you already know these so I will run through them very quickly. But basically DNA extension reaction is incorporating a base onto a growing strand of DNA using a DNA polymerase. You may hear conversations around engineering DNA polymerases or changing that enzyme so that it can better handle

fluorescently-modified bases for example but this is a naturally occurring enzyme that is used to extend DNA.

Nucleotides are the building blocks of DNA; A's, C's, G's and T's, and they can be fluorescently tagged and incorporated into these growing strands. And so if you see a green label for example, that might mean you have incorporated an A; if you see a red one it might mean you have incorporated a C. These are visualized using laser imaging strategies, and I will not go into a lot of that, but you can either image a single base being incorporated or you can take a picture of a whole set of different bases being incorporated and deconvolute that image later.

Fold-coverage is a really important term. This is a term that means the number of times you have sequenced a region of the genome in a specific sequencing assay. The more times you sequence a region of the genome, the better idea you have of accuracy; the accuracy improves with fold-coverage. And the more fold-coverage you have, the more gaps you cross in the genome and I will show you an example of those.

Read length is important because short read lengths are difficult to assemble to the genome, the reference sequence of the genome, so that may stick in three or five different places. And these short read length sequencing technologies do not let you see larger structural events in the genome and so people like longer read lengths in general.

Paired-end reads is a technical solution to get around short read lengths. I will not focus a lot about that but you may hear that term where you take a large fragment and you sequence the ends and then you can pop that up against the genome and you know where those ends came from.

A library is basically taking the human genome and shattering it and then putting it into a genome sequencing reaction. So it is a term that means lots of small fragments of the human genome.

Partitioning or genome selection is an important concept. So rather than shattering the whole genome and putting it into a machine, you now pull out very selected regions of the genome and just sequence those. So you can sequence just one gene or a set of genes or just the exons of all of the genes from the genome and this allows you to sequence what you want to sequence at reasonable cost.

Cost per base, I think that is intuitive, cost per genome.

Accuracy is a critical metric that will come up over and over again throughout this afternoon's series of talks.

Throughput, so how much can you push through a sequencing machine in a day or in a run? How many bases or megabases or billions, gigabases, of sequence can you sequence in a specified period of time?

Assembly, how do you take the output of sequencing a

library or sequencing a region of the genome and assemble it into something that actually looks like a strand of DNA or a chromosome or a fully assembled genome?

Storage, there is a ton of data. You need lots of storage and computational infrastructure.

And then interpretation I think is probably the vaguest term I have on here and I will let the real experts, Paul and Charis, talk about that perhaps in the question and answer period.

(Slide)

First-generation technology, I will be brief. Basically this is capillary electrophoresis using a Sanger technology. There is one gold-standard platform that exists in the world. Pretty much every DNA-based molecular diagnostics laboratory uses this; this is the Applied Biosystems capillary electrophoresis machine. If you talk about DNA-based diagnostics in a CLIA laboratory setting, think BRCA1, BRCA2, CF, whatever it is, this is the machine that it is run on. It has incredibly long reads; it is the gold-standard. It can only sequence very targeted regions of the genome, it is very expensive but it has very high accuracy; first-generation technology.

(Slide)

Second-generation technologies; basically these are the technologies that are being used in the research space.

These are platforms like the Life Technologies SOLiD 3, SOLiD 4 and SOLiD4HQ platforms, the Illumina HiSeq platforms for example that are run at the Broad and the Beijing Genome Institute, George Church's freeware sequencer called the Polonator, and the 454 platform as well as the Complete Genomics platform.

These platforms can sequence, again, libraries of fragments that can generate millions to billions of sequence in days which I guess if you think about it could be fast or could be slow but they in general have short read lengths, 454 being the exception, that often make assembly difficult. They are plagued by moderate error rates, let's say error rates of 1:1000 which if you think about sequencing a 3 billion base genome, leaves you with 3 million errors across the genome that clinical geneticists are left to wade through and interpret and are essentially false positives.

So the notion here is that you can get a genome but it is not perfect and data analysis, because of the short reads, is difficult.

(Slide)

There are basically two different types of assays; this is maybe overkill for an introductory session. There are assays around emulsion PCR and there are assays around bridge PCR. Basically this is the Illumina assay. This is the assay all of the other second-generation technologies use where you

take your library, you put each fragment into a little fat bubble, and then you do the reaction in this fat bubble and then you land them on a microscope slide and you have hundreds of thousands to millions of these little bubbles that you are imaging in real-time as they extend.

Bridge PCR is basically you take the library and anchor it on the slide, you do all the reactions right on the slide, and then you image them; just variations on a theme.

(Slide)

So there are strategies here and I mention this again, genome partitioning and genome selection. So if you do not want to sequence the whole genome, you can just capture the regions of interest. And there are really two different ways you can do that. One is a hybridization-based technique manufactured by Agilent where you take short synthetic strands of DNA, single-stranded strands of DNA, you shatter the genome, you mix them together, and you suck down those little synthetic strands with magnets and you have captured whatever you want out of the human genome.

The other is a technology called RainDance which again uses those little fat bubbles and you can amplify a very specific region of the genome using the polymerase chain reaction and output that and put it right onto the sequencer. Two different strategies for just picking what you want and sequencing it.

(Slide)

Current generation, let's say second-generation technologies, there really are two front-runners right here in the commercial marketplace. One is the Life Technologies/Applied Biosystems SOLiD 4 platform and one is the Illumina HiSeq platform. We will see very shortly that these platforms will be able to sequence about 300 gigabases of DNA which is 100X-fold coverage of the human genome so you can sequence roughly 3 genomes at 30X coverage which is the coverage you need to have a complete human genome. So let's say 3 genomes in a few days on either one of these platforms with average read lengths of about 100 base pairs which is reasonable for assembly purposes.

(Slide)

If you look at accuracy which is a key metric that I think we are all going to need to keep in mind as these technologies evolve over time, you will see the number of colored ticks in here represent errors. You see here, for example, the current Life Technologies platforms have accuracy rates of about 1:10,000 relative to other platforms which might have accuracy rates of 1:100 which lead to tons of false positives and can really lead you to tell someone they are going to die of a horrible disease when they will not.

(Slide)

Finally third- and fourth-generation technologies; I

will not belabor these but they are single molecule technologies where you actually put a strand of DNA into a tiny little channel, you can measure single fluorescent nucleotide incorporations in real-time using a detector that sits in a zero-mode waveguide for example; this is the Pacific Biosciences platform. Helicos has a similar platform except they just tether a single strand on and watch the fluorescent nucleotides incorporate.

(Slide)

And then the fourth-generation technologies which are probably between one and two years out from commercial use, really promise to get a genome at a very low cost and these are companies that you will hear about, for example, Oxford Nanopore which threads a nascent DNA molecule through a channel here and you can measure conductance changes based on bases that are added. Ion Torrent which is the worlds smallest pH meter, again non-fluorescently labeled nucleotides, a normal polymerase grabs an A, incorporates it, and you see a pH flux here and that is how you know you incorporated the base. Genia which is another single channel pore company and NABsys which is another solid-state technology.

Here the promise is very long read lengths, dirt cheap; we all know how much a computer chip costs to manufacture, that is essentially the type of substrate we are

using here, potentially low error rates but we don't know that yet and they are largely unproven.

(Slide)

Lots of data; petabytes of data. One petabyte of data can cost between $100,000 and $1,000,000 just to store and then you think about processing all of this data and suddenly you are in a data nightmare.

(Slide)

And then how do you interpret all of this data? We have put forward a solution called Navigenics, I am not going to talk about that today, where you can get a sample, run a genome or part of a genome, deliver that to a person's doctor and at the point of care interpret that in a scalable way. There are other folks who are working on this problem, Omicia, Knome, Personal Genome Project, et cetera.

But this is the real challenge. Once we get to the price points and accuracy in third and fourth-generation sequencing technologies, how do we make sense of it so we do not hurt people yet extend the healthy lifespan and reduce suffering; so I will end there.

(Applause)

DR. BILLINGS: Are there any brief clarifying questions for Dietrich?

(No response)

DR. BILLINGS: I guess you were clear.

DR. STEPHAN: Thanks.

DR. BILLINGS: The next speaker is Cliff Reid who is Chairman, President and Executive Officer of Complete Genomics. Cliff got a B.S. in physics where there is not much B.S. from MIT, an MBA from Harvard Business School, and a Ph.D. from that second-rate Stanford University Systems Engineering place. Cliff has had 25 years of working in growing companies and he will discuss with us the accuracy of whole-genome sequencing, the magnitude of the data generated, and how that data, at least initially, might be best managed.

Quality and Management of WGS Data

by Clifford Reid, M.B.A., Ph.D.

DR. REID: Thank you and good afternoon. Thank you very much to Paul and Charis for giving me an opportunity to present here with you today.

What I am going to do, very briefly, is really talk to you about two topics that will really drill us down a bit into the topics that Dietrich has already introduced.

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The first topic will be about the quality of whole-genome sequencing and the second will be about managing the data around whole-genome sequencing.

And I am going to discuss really the same topics in each of these two categories. I will make some simple observations and do just a very few calculations for you that

I think are illustrative and then discuss the implications for both discovery research and for clinical applications.

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First of all let's dive into whole-genome sequencing quality. And the main thing I want to do here is contrast the quality of a whole human genome with the quality of a targeted test of a genetic marker.

And these are fundamentally and profoundly different things. And the profound difference comes from the fact that markers are measured but genomes are calculated and they always will be.

So let me just kind of walk you through the process of sequencing a complete human genome. All of the technologies, actually all of the first-, second-, third- and fourth-generation technologies apply the same three steps to sequencing a complete human genome.

The first step is to break up DNA into fragments and this is actually a requirement imposed upon us by Mother Nature because we do not know how to take DNA out of a cell without breaking it up so it naturally fragments itself. So this is not a deficiency of current technology, this is going to be something we will live with for the next decades to come. So once we have all of these fragments of DNA, we make measurements of them using whatever technology happens to be available. And then what we have to do is take all of these

individual measurements which consist of a series of A's, C's, T's, and G's ranging from a few tens of bases up to a few thousands of bases and we have to jigsaw puzzle the whole thing back together again.

First on the measurement side, all measurement technologies at this molecular level have some error rate. They used to have very high error rates; they are going to very low error rates, but they always have an error rate. We don't have the physics to exactly measure the molecules and again I do not think we will for decades to come. And today the kind of error rates you see are 1:100, maybe they are 1:1000, a little bit higher, a little bit lower but the essential point remains that all of the measurement technologies have an error rate.

So the act of putting these measurements back together again has been informed by some very well understood methods out of information theory. And it is how do you generate a reliable result out of unreliable measurements?

The reason our phone system works, that you can talk over the phone and the other person can hear you, is because of this information theoretic concept. Because when we talk on the phone, what happens is our voice is cut up into little packets, it is broken up just like the genome is broken up, it is sent over a network and then it is reassembled on the other side and invariably some of those packets disappear. Yet when

we talk on the phone we hear each other perfectly. What is going on? That is the power of information theory.

Because what we do is we incorporate redundancy into the phone networks so that when your voice is sent across the wire, it is actually sent with redundant information so that an unreliable delivery channel results in a reliable signal getting to the other end. This is a fundamental concept that our phone networks are built on, our email networks are built on, and most complex systems are built on some form of this concept. And we, the scientific community, have built DNA sequencing on the basis of this same concept. And it is not going away; it will continue to do this.

So today, we typically use a lot of redundancy. Your CD player, by the way, is an E to F redundancy, 8 to 14. For every 8 bits of information on your CD player, they code it in 14 bits so their redundancy there is just about a factor of 2 to be able to play a movie on a CD player because that is an unreliable channel.

We use a lot more than a factor of 2 in DNA sequencing because our underlying measurements are still pretty low accuracy so we use a factor of 20 to 40 redundancy to wash out the errors.

So because we are doing this calculation using this information theoretic construct, we are able to take these unreliable measurements and produce reliable results.

Now the total accuracy of the calculated result really depends on three things. It depends on the quality of the underlying measurements, so the higher the quality of the measurements the more accurate the result. It depends on the number of the underlying measurements, the amount of redundancy, because that enables us to wash out errors in the process. It is kind of a voting process, you know, voting the bad guys off the island and leaving the good guys on. And it also depends very importantly on the quality of the software because unfortunately these voting strategies are not closed-form; there is not one right answer. There are a lot of different voting strategies that can be applied to produce high-quality results from low quality measurements.

Let me give you an idea of the complexity of our software at Complete Genomics. I just checked yesterday, we have about 1.75 million lines of code just in the assembly. We have about 10 million lines of code throughout the system. But this voting algorithm is about 1.75 million lines of code. Wow, how do you validate that? The only way to validate it is by looking at the output and making sure it is right. And within that code, and within any assembly software in the community, you can decide which kind of errors you want to make. You can trade-off errors of commission from errors of omission; false positives versus false negatives. So the software is very complex and will remain very complex for the

foreseeable future.

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Now what does this mean in terms of actually sequencing a genome? So again, following with a few of the nice comments that Dietrich has made -- so first of all let's start right here. The most accurate human genome that has ever been published was published in *Science* right at the beginning of this year. It had an error rate of 1 error per 100,000 bases; that is a 10^{-5} error rate. What does that mean? So we kind of flow that through a genome. There are 3 billion base positions in the genome, it is a diploid genome, there is 6 billion, but we will call them as diploid calls here. So if you flow -- randomly were to assign 1 error per 100,000 bases throughout a 3 billion base genome you would end up with 30,000 errors across that genome.

Now a lot of the genome is not very important. It looks likes half, maybe two-thirds of the genome, does not do very much. But in particular, there is 1 percent of the genome that is very important and that is the part that codes for proteins. So for the purpose of this conversation, let's not talk about promoters and other conserved regions, let's talk about the part that codes for proteins. If we were to spread these 30,000 errors sort of randomly through the genome, we would get about 300 errors in the coding regions and that would be an error, meaning 300 errors in each of

about 30,000 genes. The current number is 20,000 to 25,000 but some ongoing research says there are probably a bunch more in there we just have not found so I use 30,000 genes. This says about 1 percent of the genes are going to have an error in them.

Now for research purposes that is terrific. And the reason is because in a research study you will take 100 samples; and if you go to any single gene, if one percent of the genes have an error, the probability that in a given gene, and even 5 of the 100 copies of that gene through your 100 samples in the research study have an error, is 1 in 10 billion; it is zero. So again this sort of --- of large numbers works out that in the research world these kinds of accuracy are excellent and enable us to draw correct research results from data that has an error in something like 1 percent of the genes. This is completely unacceptable for clinical use; so that is where we are today. The best genome in the world published is completely unacceptable for clinical use.

Because of this was your genome and 1 percent of the genes were wrong, you would say “thank you but no thank you; I am not going to go down that path.” As a result, today in the clinic, we need to independently validate. We need to use these very expensive technologies that Dietrich referred to to go back and verify every change in the genome that we think is

medically important and that prevents it from having high clinical utility. So the question is what would it take? What would it take to make whole-genome sequencing a clinical tool? Well that is a judgment call and this committee and other policy setters are going to have to come to some conclusions about that.

(Slide)

But let me make a modest proposal. Let's propose 1 error per 10 billion bases so that says drive the error rates from 10^{-5} down by a factor of 100 to 10^{-7}, what would happen then?

We take this new error rate, this 1 in 10 billion base error rate, flow it through a genome. 3 billion base positions, that corresponds to 300 errors per genome. Now flow it into the 1 percent of the genome that codes for proteins, that is 3 errors in the entire coding part of the genome. That says an error in about 3 of about 30,000 genes that says it is about 99.99 percent accurate. That is starting to be a clinical result. I would say that probably is a diagnostic quality result for many applications though certainly not all.

So how long is this going to take? Here I am much more pessimistic than Dietrich. I build these systems and he runs them okay. I think that we are going to spend between two and four years before we see a 10^{-7} genome come out of the

industrial community. I think it is going to take that long and I think that is going to happen in a laboratory environment with industrial strength equipment and super computers and people in white coats walking around really enforcing regulations. Before that happens, point of care, before that happens in a hospital, for a same day turnaround I think you double it. I think you are probably six to maybe ten years away before we are going to see those kinds of clinical results. So there is a time delay built in here.

One of the key challenges is, you know, if you have over a million lines of software and every genome is different, how do you validate it? How are you really sure that those things are right? That is going to require a very heavy-weight validation environment to make this all come true. We are on our way but I think in the reference lab model, which I think is the model that clearly is going to hit the market first, we are sort of two to four years away before these are going to be really clinical quality results.

(Slide)

Now let me change gears on you and stop talking about the quality of the genome and start talking about its size. There is a lot of conversation now about the size of the data but I think that there is something that is being overlooked here. In fact I think this is a -- this was not a problem two years ago because none of the instruments could

produce enough data to cause it to be a data management problem and this will not be a problem in four years.

We are in a bubble of a problem which means if we just ignore it, it will go away and we all love those problems and let me describe for you why.

So here is the flow of data through a DNA sequencing instrument and all of them flow basically the same way. And what I have characterized for you is the size in gigabases and then to put another metric on it, the dollars to store that amount of data using the Cloud and this is the Amazon Web Services S3 system.

So when you sequence one complete human genome, the images that come off of that genome, that is really the raw data, these are imagers, these are microscopes that take color pictures at their heart, right. The images that come off of this data is about 3,000 gigabytes so this is 3 terabytes of image data. To store that on Amazon for a year costs about $5,000. So to store a genome for a few years costs more than it does to sequence it. It is a very important observation we will come back to.

But that is the raw data and in fact the raw data in our system, it never even hits a disk drive, it is so big that we just process it on the fly, on-the-wire processing. So as the images are coming off the instrument, they are never stored. They are converted into a much more compact format

before anything ever hits the disk drive otherwise it would be economically prohibitive to run these sequencers.

The next phase of storage is the reads. So these would be 50 to 100 to 500 to 1,000 base sequences of A's, C's, G's, and T's that map to those individual physical fragments of the genome. The reads are about 10 times smaller so to store them for a year costs about $500; okay, now we are beginning to talk, right.

Then comes the genome itself, 6 billion bases because two parental chromosomes of A's, C's, G's, and T's; another factor of 10 smaller. That only costs about $50.

But here is the real rub. You do not care about 6 billion bases of A's, C's, T's and G's because there is a reference genome, it is called Build 37 of the NCBI genome, and we are 99.9 percent the same. All you care about is the variants. You want to know what is different between the sample that you are sequencing and what is published at NCBI.

So if we go in and look at the variants, the differences between the genome, that is about 300 megabases; it fits very nicely on your thumb drive. So where is the data management problem here? Why is there so much conversation about data management? The reason is this. People do not use the variants right now, they want the reads. Why do they want the reads? Because there are errors in the variants and the reads explain the errors. So the reads enable a researcher to

say “Hmm, this one looks suspicious, how did you get it?” Now he does not want the raw images because you would say “here are the raw images, go write an imaging pipeline” and three years later he would have an answer to his question. But he can go back to the reads, the A’s, C’s, T’s, G’s, and stack them up and look at the voting and say “Ah, I am not sure I like that one” or “oh, yeah I get it now.” So reads are being kept along because people do not believe the variant data is good enough and that is about to go away. Because as soon as we go from a 10^{-5} to a 10^{-7} assembled error rate, the reads are useless; they are nothing but supporting information. All of the biologically important information, for research or clinical use, is captured in the variants; we just do not trust them yet but we will.

And in fact our customers are moving toward variants only. When we sell genomes, we sell variants and we sell reads and half of the customers buy the reads and the ones that do tend not to look at them because the variants are getting plenty good enough for research purposes so that they can make good research discoveries without ever having to mess around with this huge collection of data that would cost $1,000 to store for a couple of years.

But the final comment is that pretty soon, as the cost of sequencing comes down, it is going to cost more to store the data than it will to resequence it. And what that

means is that DNA turns out to be an incredibly cheap storage mechanism; cheaper than bits on a platter. So we are on the way to having this data management problem go away. It is with us today but it is disappearing.

(Slide)

So quickly I am going to wrap up. Another version of data management is the interpretation data which Dietrich mentioned. There are two kinds of interpretation data. One is variant data, what is going on inside the genome, what are the interesting variants. I had pulled a number out where in one of the variant databases, this is dbSNP, the simplest of the variants, these are the common SNPs, there are about 23 million entries in the variation table in dbSNP. It is not curated; we do not know which ones are right. It is growing rapidly and whole new categories of variants are coming on line. This is where the data management problem lies. Do not worry about the genomes, worry about the interpretation data; this is the stuff that needs to be curated properly.

Similarly the scientific literature about what those variants mean is largely uncurated. We know a lot of it is wrong. It was done early with early technologies, many times with under-powered studies. So this ends up being the more interesting of the data management problems as we project our thinking five years into the future.

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Many other issues that I am not going to touch on today, some have already been touched on and we will talk about some more in other talks and then maybe in the Q and A session. But validation, as was pointed out, the different whole-genome sequencing methods give different results. Which one is right? Well they all make different mistakes. With normal genomes, we can go back using very expensive sub-setting methods and spot check and that works pretty well but with cancer genomes it is much harder because the spot checks do not work very well so cancer genomes have their own set of challenges.

Quality control remains a big issue. The whole 23andMe thing of rotating the plate, you know, that is a simple procedure; whole genomes are a lot more complex.

The knowledge bases are I think -- among the key issues around curating them and then starting to get them out into the world.

And then electronic health records, we are getting this data in some standard format, secured properly, distributed around.

You know, huge issues around data quality and data management but the actual body of genomes themselves really I do not believe we are going to have much of a data management problem with it all.

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So my conclusions, first of all on the research side, the revolution is underway. We are taking orders for thousands of complete human genomes now and the discoveries that are going to take place with this are going to be I think extraordinary. The data management problem is on the way to solving itself through variants becoming so reliable that the datasets become very small. And in the interim, some outsourcing and some file computing; you know, thank goodness that Amazon exists so we all don't have to go buy those disk drives.

And then on the clinical side it really breaks into two areas. On the marker side, the targeted test side, we are just going to see the golden age of targeted tests where we have now moved out of the area of common variants and into the area of rare variants and that is really where we are going to see, I think, the major discoveries made. And then once the discoveries are made, wonderfully it is easy to deploy because those are markers; they are easy to measure, they are easy to look up, easy to figure out what they are, and easy to take action. So we are going to kind of see the golden age of genetic markers now moving into the clinic.

In the whole-genome sequencing arena I think there are really just two future applications we see clearly on the horizon. I am sure there will be others; we will figure it out as we go. But two that we see clearly are first and

foremost being cancer genomes. Cancer genomes are so messed up. We just published a cancer genome with Genentech and it is mind-blowing what is going on inside the cancer genome. That is going to be an arena for whole human genome sequencing for a long time to come. Markers are not going to tell us what is happening inside a cancer.

And then the other one which is full of controversy, full of issues, full of policy decisions that bodies like this are going to have to help the community make, is the universal genetic panel; 6 billion bases of accurate DNA in each of our health records that we can look up when we need.

So we are in the heyday right now, completing the genome sequencing, costs are down, quality is up. The research community I think is going crazy and it is not far before the clinical community picks up and runs with it.

So I will stop there. I do not know if we have time for questions.

DR. BILLINGS: Question Elizabeth?

DR. MANSFIELD: Thanks Cliff, a very good presentation. I have a couple of questions that -- tell me if this needs to be held until the discussion at the end. But how do you actually determine accuracy? What are you comparing to?

DR. REID: Today the way that the community determines accuracy of a complete human genome is by spot

checking it. And as Dietrich mentioned, if you go back to first-generation sequencing using Sanger sequencing on an ABI instrument, you can get a very good, highly accurate, orthogonal result. So you go in and you spot check the genome. In fact we look at the most suspicious places, the places that are not "yeah this looks just like the NCBI reference" but the place where a technology thinks it found something novel in this genome. We go back to the original sample, snip that DNA out of the original sample, send it off for small but very expensive sequencing, and see how many mistakes the new technology made and that is how we calculate those numbers like 10^{-5}.

DR. MANSFIELD: Okay, and you mentioned that different platforms give different kinds of errors. So the errors are not random, they are not independent?

DR. REID: They are not random and they are not well characterized in their systematic effects. We know the Illumina platform has great difficulty analyzing insertions and deletions. And we know that the Life platform misses on 2 base SNPs. But that is the little we know about the systematic errors in the platforms but there are systematic errors. I think everybody selling an instrument has to step up and admit that there are systematic errors. We sell data, we do not sell instruments, we step up and admit there are systematic errors. We do not know where they are yet, we are

a younger company, we are figuring that out. But there are errors in all these platforms and there will continue to be. And when their Nanopore system is doing it, there will continue to be; you get into quantum mechanical effects when you start measuring these things. These are 100 Dalton molecules, one-third of a nanometer across. We are decades away from having the physics to hold these suckers down and measure them. So we need to live in this world of exploiting this last 50 years of information theory to generate reliable results from unreliable measurements and we can do that to health quality and I am confident we will.

DR. MANSFIELD: So will fold coverage actually resolve those errors or do you just have to know --

DR. REID: If they are systematic, fold coverage does not resolve the errors; that is exactly right. And then what you need to be able to do is characterize those errors and then say whenever you have a disease determining variant that has that characteristic, when it is whole-genome sequence, you say “invalid,” grab that piece of DNA, send it over to the ABI box, sequence it, now we have a valid answer. So we can construct a valid system without each individual component of it being perfect.

DR. BILLINGS: Thank you Cliff.

DR. REID: You are welcome.

(Applause)

DR. BILLINGS: The next speaker is Martin Reese who is Chief Executive Officer and co-founder of Omicia which is an advanced software company bringing whole-genome information into healthcare.

Prior to founding Omicia, Dr. Reese founded a company called Neomorphic. It was the seminal development of human annotation software by Neomorphic that provided the foundation of successful commercialization of microarrays by Affymetrix.

Martin is a championship ping-pong player, a Warrior fan and a Bears fan and foolishly supporting Germany in the World Cup. He will speak today on how whole-genome sequencing data are annotated and presented in the clinical setting.

Preparing and Managing WGS Data for the Clinical Setting

by Martin Reese, Ph.D.

DR. REESE: Thanks Paul for the very nice introduction and thanks Charis for inviting me to speak today. Paul and Charis asked me to give you a little bit of an overview of what we can do. They asked me to talk about preparing and managing whole-genome data.

And this was wonderful for me because the first two talks were all about how to generate data, the data quality, and I am trying to run you through some issues if you have the data and what to do with the data.

(Slide)

So the biggest challenge really is, and I really 100 percent agree with Cliff on this one, is how to distill a genome's worth of data? Very soon in the future we will have thousands of personal genomes, we have the 3 billion base pairs, we have 4 million variants for each individual genome, 4 million is really the number roughly that we have to try to interpret, 23,000 genes, and then a vast amount of disease literature today that people have worked on.

So the big question is how do we take personal genome sequences all the way to diagnostic and prognostic summary?

(Slide)

So to put it in context again, what I am going to talk about -- we have heard a lot about the sequence generation, the machines, how to make it; we had a beautiful introduction there. This is just getting the sequence out. Then what we call traditional bioinformatics which is all about assembling, all about alignments of these reads, and base calling; this is basically this idea of getting the quality of these individual reads right. And then what I am going to talk about today is the analysis and interpretation of that data.

If I talk about that, what do I mean? First I mean annotation. So if I have 4 million differences, I have to put some kind of knowledge from the databases on these individual

variants. Second, there is information about variants in the literature, in publications, so I can use that as clinical integration. And then what I need to do is then I need to take this and generate reports. This is what I call technical interpretations of complex genetic and genomic data. So this is what we call the analysis and interpretation of a genome.

And then ultimately, of course, is the clinical interpretation and the clinical utility but that comes basically on top of if you sort of have a genome report.

(Slide)

So what I am going to do is I am going to focus on three main things which is the genome quality and we have heard from Cliff a lot about this right now; and then second the integrated approach that is really needed to make any sense out of that, and then lastly the clinical interpretation.

(Slide)

So the way I am going to do this is I am going to walk you through an experiment that we did where we just used the publicly available first 10 genomes that were available in the public domain. So first of all thanks to everybody for giving us that information.

So here are the 10 genomes and what we see is the ethnicities are nice with different ethnicities and beautifully we have six different platforms that these

individual genomes were actually sequenced on. These are the original publications. So as you can see this is from 2008, 2007, 2009, so again this is publicly available data already one or two years old so we need to be very careful because technology is moving so fast so the error rates and everything are much better today.

(Slide)

But let's assume we look at the genome data. So the first thing we do is we compare a new genome sequence with the reference genome, we talked a little bit about that, and then what we generate are these variant files. And I again 100 percent agree, all we really need to do is compare variant files with each other. If we do this for these 10 genomes, we see a very nicely structured tree.

(Slide)

Now if we look at the ethnicities, you see that the Caucasians cluster, African American, and Korean and Chinese cluster. So from a very high level, 20,000 foot view, what we can say is all these different genomes sort of make sense from a historical point of view.

(Slide)

And that, of course, is very encouraging because all the different technologies as you can see -- and we still get that very nice tree. So again, if we look at a very high level, that looks pretty good.

(Slide)

Now we do have the opportunity, because there is actually one genome that is the same individual that is sequenced twice on two different platforms, so what we can do now is we can actually look in detail at what are the differences between these two different technologies.

And what you can see here, if you look carefully, there are actually 500,000 differences between two different genomes and again these were the first two published genomes; so this is from the public literature.

Now another one that actually illustrates the complexity that we are facing very soon is look at the total number of variants, 3 million; 3 million and here 4 million. And these are just the single nucleotide variants. These are actually the easy variants that we have to use and interpret. So the complexity of really interpreting 4 million is just astounding.

(Slide)

So as I said, 3.5 million variants and these are the easy ones. We have indels, we have structural variants which were, again, the systematic errors that we are not even touching today, to try to interpret. What that translates into, and I am just using this sequence as if it was correct, we have 21,000 coding variants. These are variants that each of us is carrying in the human genes. So that is what we are

going to tackle first.

(Slide)

So the first thing you can do is you can look at well-known databases and try to see what we can learn from that. Just to give you some scale, this is the Online Mendelian Inheritance in Man database with a lot of the Mendelian genetic diseases. And what we have is we have roughly 2,000 genes, this is from last year but the scale is pretty much the same, and then within there we have actually 15,000 allelic variants that have been described in the literature and curated into this database to be of clinical or genetic relevance; so 15,000 is what is in that database.

(Slide)

Actually funded by a SBIR grant from the NHGRI, we wrote a lot of software to now link these disease variants in the genome to our reference genome. And then we can ask the questions for these 10 individual genomes, what do we actually see?

And here is what you get. You get roughly 100 of these variants that have some clinical function are present pretty much in each of these 10 first published genomes. What we see is a heterozygous state at roughly 60 and then 30 at a homozygous state. Of course that was surprising because we thought oh, OMIM has a lot of the rare genetic diseases in it and it should be very severe. All of these first 10 genomes

are healthy genomes in healthy individuals so we were a little bit surprised by that.

(Slide)

This is just a summary of these diseases. These are severe diseases but they are all multigenic diseases and that again shows the complexity of interpreting whole genomes.

The good news is in all the OMIM disease alleles, we did not find any childhood fatal disorder variants but again we only looked at 15,000 of these OMIM variants so that is basically the first result that we got.

(Slide)

Now if we think about this, we have 21,000 coding variants, 10,000 that are actually changing the protein sequence. So these are sort of the most important ones to look at; the most interesting ones at the very beginning. One hundred of them overlap OMIM, so the question remains what to do with the next 99 percent?

So there are a lot of variants that each of us are carrying that have no obvious disease classification.

(Slide)

The next thing you can do is you can actually go into the literature to build a knowledge base and basically pull out all the genes that have been linked to diseases. We did this and then what we did is we actually built an ontology and then we rolled it all up into the Harrison's Principles of

Internal Medicine textbook for diseases in general and we rolled up all the genes from the literature into that. Obviously in a pretty crude way, but we tried to be as accurate as we can.

So this is sort of a distribution of the genes in the literature rolled up into the Harrison categories.

(Slide)

So if you do that, what you can then do is you can then basically look and look at the plot for each of these 10 individual genomes and what they are carrying. And you see within the 10 genomes, there is more variation in the African genomes but that might be due to the fact that we are comparing African genomes actually against the reference genome. Now the reference genome itself was mostly assembled using Caucasian samples so there might be actually a bias in our variant files. But in general, you can actually look and we call this the genomic load of variants.

(Slide)

Now if we now look more carefully into one individual genome, what you can see here, again here are the Harrison categories of diseases and this is the total number of genes per category and then this is the protein sequence changing variant load that we can find in this individual genome.

So I think this demonstrates pretty clearly how

complicated it will be to try to interpret this. Again this is only in the disease genes.

(Slide)

So critical, the first thing you want to do is a criteria for ranking and interpretation. We cannot interpret a full 3 million, 4 million variant genome; we need to start ranking.

One way of doing this is by the quality of sequence. So if we have a region that has a low quality, clearly we should not pay too much attention to that. The next thing is by zygosity, homozygous/heterozygous, depending on the genetic model. And then also very importantly is by protein function. So this is, I think, where we will start doing genomic medicine first which is by looking at mutations, loss of function mutations, in these genes that really fundamentally change or even delete a gene or a protein sequence so this is what we are doing the most. Again these are mutations that you carry that we have not seen before.

The next thing then is to look actually at what is known in the literature. And Clifford showed you a database about dbSNP. Now dbSNP is just a database of all the variation; there is no clinical information with it. These are sort of the most prominent databases in the public domain where we have variants with some kind of clinical information from the literature, mostly curated. The OMIM database, the

HGMD database, the GWAS data is from the GWAS studies at the NHGRI, it is updated weekly and it is a great resource, and then the PharmGKB which is the pharmacogenomics database. And as of yesterday, I checked it; there are 3,000 variants that are somehow linked to pharmacogenomics and to drugs.

So it is very important to do that. But if you do that, again, we generate a very, very long report of clinical information.

(Slide)

So what we can ask, of course, is disease predisposition, adverse drug reactions, drug responders, and prenatal risks. So now we have sort of the full report on a genome and now we sort of need to structure that and you can ask multiple and different questions about that.

(Slide)

So these were three very recent examples that are happening right now. And we talked a lot about cancer sequencing; this is a paper by Rick Wilson and Elaine Mardis where they sequenced the first cancer genome. So I am also thinking it is going to be very interesting on the cancer applications. This is about somatic versus germline DNA, so it is a little bit of a different approach and different analyses are needed for doing interpretation.

This one is the rare genetic diseases; it is a family where both kids had two Mendelian genetic diseases.

And in this study what they did is they actually found both genes. One was known before with that disease and one was unknown, so they actually could clarify that disease. So this is a fantastic area where we are going to focus in the next two to three years of a lot of interesting results and research coming out.

And then the last one was the paper in the *Lancet* which I think really lays out the landscape. If you have a full genome sequence, how do you start the clinical assessments on that? And what was nicely done is a lot of medical doctors and geneticists had to work together to just start doing some kind of interpretation.

(Slide)

So this is another example where we just recently got involved. This is the Genomic Cancer Care Alliance and in the public comments we have heard a little bit about it. It is sponsored by Life Technologies and it is about cancer patients in late stages.

Again a lot of clinical collaborators in that Alliance and we were asked at Omicia to help with the data flow and the interpretation of the workflow and this is just an overview of what we need to do in terms of data integration and data interpretation.

And again, very importantly, here is the tumor board so we are basically trying to get ready to do this technical

interpretation which is sort of coming from us, from geneticists, and computer scientists that are generating these reports, summarizing it to the most important findings for one patient, and then obviously it has to be reported to a tumor board which then can look at that data.

Here is the validation step, Clifford mentioned that a lot. That because of the accuracy of the data, because of the accuracy of sequencing right now, we still need to do a lot of CLIA validation for some of the key findings before we actually can do some clinical interpretation. But again, I think it is very important that we start building these systems today, we get going on this, because the technology is moving fast.

(Slide)

Here is another example, obviously, which is one of the very well known ones, the Warfarin gene VKCOR1, and I like this one. This is again for one of the genomes, just made up. And what you can see, it is not like you have the gene or you do not have the gene. There is actually a rule-based system among these five markers that you have to interpret which is in a paper and in the guidelines and you have to interpret that. And for us that means we have to build rules so that when we do this, we actually implement a rule which can then go into the clinical setting as a technical report for these pharmacogenomics applications.

(Slide)

So let me try to give you some take-home message from our work. So first of all, quality assessment and control, and I think we have heard really a lot about that from a clinical point of view. I think I would go a little bit further, the first thing is identity testing and what I mean by that is if I get your genome, I want to make sure this is really your genome so we need to have another technology, a genotyping array or some other sequencing, in order to make sure that the genome I am getting is actually the right one and again the 23andMe thing just points out to that.

The other one is concordance. A lot of times, and again Cliff laid that out very nicely, the sequencing technologies in these research papers, they report the error rates compared to concordance to DNA chips. And these DNA chips, the way they are built, they were built for single nucleotide variants, again which are relatively easy, and then they were actually picked because they were easy to assay. And we looked at some of the error rates that we had from these two genomes and it turns out they are really easy positions to query in the genome. So a lot of these error rates in concordance with this chip data, they are actually high estimates of what is going on in the rest of the genome.

Very important also, the genome is very different. Sometimes there are repetitive regions, sometimes there are

gene families, which then make sequencing extremely complicated and error rates in these regions go up. So there are differences in the quality in different regions of the genome and we are just starting to look into that.

Again, very important is the verification experiments again for clinical settings I would say. And orthogonal technology validation, again what Clifford referred to, the very expensive sequencing is clearly needed in the clinical setting but we can do that and then data security of course.

The second point is the integrated system. What we did when we did all this analysis and I can show you a lot of drawing boards and informatics that goes into that, but it is critical to do that for the variant ranking. Because if you get a full genome, you get a Macintosh and you have your whole genome, you do not know what to do. And today there are not really good tools out there to do anything. So we as a community really need to work on systems to do this, to do the ranking; what is important for you.

Rule-based systems are critical and then clearly when you have your genome, it can be reinterpreted later on.

(Slide)

From a clinical interpretation, I agree with the vision of technical genetic reports, a genomic medicine expert to actually review that, and then the information goes to the

treating physician. For us it is just a different way of supporting the individual chain here for interpretation. And then clearly interpretation within genetic and environmental background because if I see the person, I can actually look at some interesting genes that I really want to look at for that specific person which is critical, and then integration into electronic health records. Thank you.

(Applause)

DR. BILLINGS: Questions for Martin?

(No response)

DR. BILLINGS: Thank you Martin.

DR. ENG: All right, moving right along, we have Greg Feero who is currently the Research Director of the Maine-Dartmouth Family Medicine Residency Program in Augusta, Maine. And so his clinical practice is in rural Fairfield, Maine.

I first met Greg when he was Chief of the Genomic Medicine Branch at NHGRI and Senior Advisor to Francis Collins at the time. And he gave a very erudite and understandable talk to --- on Genetics 101. So knowing that, I invited Greg here to speak to us. Because now that we have all the data, we know how to handle it, the data is there, now what does the doctor do with it. So he will tell us about what does the doctor and various stakeholders do with it including, very importantly, the patient.

Approaches to Using WGS Data and Clinical Utility

by W. Gregory Feero, M.D., Ph.D.

DR. FEERO: Thank you and thank you all for having me back in front of you. So as I have said to you before when I have come before you, it is often difficult to decide which hat I am wearing at any given moment in time. And I think today for the first part of my talk, I am wearing the guy from the place where no one lives hat, which is in fact actually where 95 percent of healthcare occurs, outside of academic medical centers.

For the second half of the talk I am probably wearing the National Human Genome Research hat in an unofficial capacity.

So I also think I drew the short straw for my talk today. She did not say that in the introduction but I get to talk about clinical utility which everyone has a difficult time with handling.

(Slide)

So I think there are a lot of my slides in the packet. It is a little hard with this many speakers together to not have too much redundancy, kind of cover things that went before, but suffice it to say, we are in a period of time where the technologies are allowing us to sequence DNA in an every increasing pace and at decreasing costs. And this series here essentially just relates it not in terms of cost

but in terms of time for sequencing and these third or fourth-generation technologies are allowing sequencing of a whole genome within a day, now within the range of reasonable cost.

(Slide)

And I just make the point that there is a push, I think, generally to try to get the latest and greatest technology out there in front of the healthcare provider and the patient. And I think we have to be a little cautious about the consequences of that push of getting this out into the environment. This is just in the last couple of weeks, vastly exceeding anyone's estimates here, the cost in the next little while for whole-genome sequencing; a company that is considering offering it for $30.

(Slide)

So there is a huge raft of questions associated with the availability of whole-genome sequencing. The granddaddy of them all is really this issue of clinical utility.

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So the outline for the talk today is two-fold; clinical utility or "I know it when I see it," and getting to utility. And I think the "I" is the emphasis in there. The utility really depends very much on the prospective of the individual and it is vastly different for a start-up company, from a researcher, from an oncologist, from a primary care clinician, and from an average patient.

(Slide)

So to define utility or talk a little bit about utility, I went back and I read a report by a Task Force that was put together and I believe actually made the recommendations for forming the predecessor of this group. And they set forth three criteria for the evaluation of genetic tests: analytic validity, clinical validity, and clinical utility. And I think we have heard a lot about analytic validity and clinical utility has been beaten into the ground, it does not mean there are still not issues.

(Slide)

But clinical utility they defined it in that report as "the balance of benefits to risks…Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results."

(Slide)

And interestingly, this issue of clinical utility -- I have been at several of the meetings where we talk about clinical utility versus personal utility, et cetera, et cetera. When you go back to this report, it is actually pretty instructive. Clinical utility in this report brought in elements of personal utility into it. Those are enumerated in the first part of the list; and at the bottom, talk about the things that most people think of as clinical utility,

improved survival, cost savings, et cetera, et cetera, in terms of risks and harms.

But clearly, at least in this report, they envisioned clinical utility encompassing aspects of personal utility.

(Slide)

So this definition of clinical utility that has sort of arisen in the world of genomics is falling into an environment, at least in primary care which is this hat of being the person from no where where no one lives, that is challenging to say the least. I think that primary care in the US right now is under a tremendous amount of stress. Our healthcare system is under a tremendous amount of stress. And primary care providers are rather, let's just say, disenfranchised with the establishment at this point in time in terms of what is going to happen with healthcare and healthcare delivery. And I think to some extent the patients of primary care providers, particularly in rural areas where I practice, are a bit disenfranchised with the leading edge of our healthcare system.

(Slide)

So what are the solutions to problems in our healthcare system from the perspective of a primary care provider at this point in time?

Well they do not actually rest, in their minds at

least, in genomics so much. They rest in sort of the bread and butter things that we know and have tremendous amounts of evidence for their usefulness in healthcare systems; just effectively doing these things in the system that we have right now, essentially simple things like measuring blood glucose, measuring blood pressures, and measuring fasting lipid panels in all the patients who need to have them measured.

So this unfortunately I think for many primary care providers is the perspective on genomics and what genomics currently brings to bear in the healthcare system.

(Slide)

Now this, obviously again this is an issue of the "I" because I think for clinical oncologists right now, particularly clinical oncologists in an academic setting, this is definitely not the case. But for your rank and file and primary care provider, you are there.

(Slide)

And worse than sort of this just ambivalence, there are folks in the primary care community who are actually sort of actively questioning the value of expending as much money as we have expended in genomics on genomics and genomic discovery due to this sort of lack of evident utility to this point in time.

And I think we have to be cognizant of this issue

when considering conversations of clinical utility in this group.

(Slide)

So these folks have a perspective that is rooted generally in the world of evidence-based medicine. And I think that, though not everyone will admit it, evidence-based medicine itself is a rather imperfect field. It has its problems. It has different definitions. This is one of the founders of the world of evidence-based medicine, Dave Sackett's definition.

And one of the things that these evidence-based medicine folks generally have in common is sort of a rigorous way of looking at the evidentiary base that supports the use of a proposed new technology, whether it is a genomic technology or a new imaging technology, in healthcare.

(Slide)

And you probably cannot read this slide; hopefully you can read it in your handouts. But this is just one of the criteria put forth in the *American Family Physician* in June 2004 called the SORT Criteria. And they essentially have a grading mechanism for the evidence that exists. And at the top of most of these evidence-based medicine ranking systems are what we call patient -- studies that show improvements in patient-oriented outcomes. And then secondary are studies that show improvements in surrogate markers. And finally in

the end are studies that really are associative and really do not show improvements in hard outcomes.

(Slide)

So what do we mean by patient-oriented outcomes? Outcomes that matter to patients to help them live longer or better lives, including reduced morbidity, mortality, symptom improvement, improved quality of life, or lower cost. So when we are considering the issue of clinical utility, I think we have to be cautious about aligning our fairly nuanced view of potential clinical utility and what the rank and file healthcare provider who is facing an ever mounting number of patients and ever lowering reimbursement and an ever growing number of things to do, and how they view the issue of utility.

(Slide)

So I put these together and they made their gross generalizations unfair, these next couple of slides perhaps, but the world of evidence-based medicine versus the world of genomics.

(Slide)

Morbidity and mortality versus surrogate markers.

(Slide)

Effectiveness versus efficacy. I think the world of the primary care clinician is much more solidly rooted in the world of effectiveness than it is in the world of efficacy.

And of course there is peril in being too firmly rooted in either of these two worlds but I think again we have to be cognizant when we are considering the definition of clinical utility of this distinction between the EBM world and the world of genomics.

(Slide)

So how are we doing in terms of matching evidence with expectation for evidence in genomic applications? Well recently, many of you are probably familiar with this conference, The State of the Science Conference the NIH held last year looking at the evidence-base for using family history, one of the oldest genomic tools known to man, as a screening tool in primary care office settings for reducing morbidity and mortality essentially for a wide variety of common conditions.

(Slide)

And the bottom line is, there was not that much evidence; in fact, extremely little evidence out there that would meet the high bar of evidence of reducing morbidity and morality.

So the intersection between personalized medicine and genomics and evidence-based medicine at this point in time is actually quite small. And I think this is a huge barrier to whole-genome sequencing looming.

(Slide)

And why is this? Well it is largely because we focus most of our attention on the world of genomics, and rightly so, on getting the early stages of the science to the point where you can begin to grapple with issues of clinical utility. So the vast amount of research expenditure occurs in this T0, T1 phase if you believe this T1 through T3; there are problems with this. It is probably too linear, et cetera, et cetera. But in fact this is where the vast amount of our focus has been. And I would argue that this is where the actual key to adoption ultimately is going to lie for these technologies.

(Slide)

So how do we get to patient-oriented outcomes? Well there is a lot of that T0, T1 work still to go. But I think increasingly we should be having an eye toward the later stages of research and beginning to prove that some of these things that many of the previous speakers have sort of assumed actually will improve patient outcomes actually do improve patient outcomes.

(Slide)

So at this point in time, I think we have already heard this, we have this change in infrastructure requirements. We are rapidly achieving a point in time where the DNA sequence production is not going to be the bottleneck for figuring these things out and gaining actual clinical

applications. It is going to be this world of bioinformatic analysis. And then sort of the next step, which is potentially a bigger hurdle, is this integration of the bioinformatic analysis into actual clinical analysis and use.

(Slide)

So I don't think I need to belabor this but we have already heard that there are a whole lot of variants out there in the genome that might be relevant to human disease. And at NHGRI in the Intramural Program, Les Biesecker is a PI of a project called ClinSeq that really drives this point home.

(Slide)

They are looking at a series of candidate genes for potential cardiovascular disease risk essentially doing limited whole-genome sequencing on these candidate genes in looking at those genes in a cohort of well phenotype subjects and beginning to look to see if they can use that information, the genomic information, to help predict risk.

(Slide)

And this is older data from the ClinSeq study but you can see there is just this huge number of variants that are popping up in the patient population in this limited sub-set of candidate genes. And making sense of what is wheat and what is chaff is going to be an incredibly large challenge.

(Slide)

So I guess I would say yes we are in that bubble

phase in terms of data storage capacity. But I think we are going to face challenges in data storage capacity all the way along from the phase we are in right now, the ugly ducking stage, through to Nirvana actually. Because at some point in time, we are going to be facing epigenetic data, we are going to be facing possibly having a cancer genome and we are going to have the germline genome, trying to track in an electronic medical record even at the stage of Nirvana. And I think this is going to be an issue.

(Slide)

And I just love this amount of storage. This is from the Washington University Center's website; just mind-boggling right now what storage capacities are needed.

(Slide)

In fact they -- this is another slide I love. They have their own substation for handling the power requirements for their data storage facility which is just remarkable.

(Slide)

So sequencing accuracy? This has already been touched on.

(Slide)

He was talking about 10^{-7} accuracies. You know even if you get beyond 10^{-7}, you still have a fair number of errors in a human diploid genome. And as we get to individualized genomes and we start grappling with these rare variants, it is

going to, I think, be increasingly hard to figure out what is actually useful information.

(Slide)

So we have this informational bottleneck.

(Slide)

We have a relatively, I think, simplistic view at this point in time of how a complex disease comes about where you have multiple variants interacting with behavior and environment resulting in disease. And really there are probably tens of hundreds of variants in some cases, probably tens of behaviors, unknown number of environmental influences that result in disease and we are just beginning to sort these issues out. So what ways will we be able to sort these out?

(Slide)

Well first we need to sort of define what we are talking about in conditions and exposures.

(Slide)

And I think for this we could look at what is going on in the world of GWAS type studies and the efforts that are afoot to come to some better definitions of phenotypes going back to something Marc mentioned earlier in the day. And you could look at an activity NHGRI has put together under Teri Manolio's group called GENEVA where they are bringing together large groups of folks interested in GWAS studies and beginning to grapple with issues of phenotyping across multiple patient

populations and it is not a trivial exercise.

(Slide)

So this issue of phenotypic harmonization can actually occur from two perspectives. One could be that you actually look across the definitions we already have and harmonize those definitions moving forward. This is equally as relevant to whole-genome sequencing as it is to GWAS studies.

(Slide)

And that turns out to be quite daunting because this is just a table for cigarette smoking, what folks have used in various studies for smoking versus non-smoking; it is really quite complicated.

(Slide)

The other approach is to sort of take a top-down approach which is where you define apriori your phenotypes and then move into phenotyping your patient populations and applying this phenotypic criteria. And this of course limits your ability to use already collected cohorts potentially.

(Slide)

So there are these two approaches and this is again an example coming out of the PhenX project for nicotine doing a top-down definition essentially of nicotine dependence.

(Slide)

So we need to talk about what variants are we

talking about?

(Slide)

We know now that single nucleotide polymorphisms, although an important contribution to variation, are not the entire game or not even close to the entire game. And we need to work on sorting out what variants we are actually talking about.

(Slide)

And I think increasingly, we get to the point where we have rare variants in relatively small numbers of people and aggregating the number of people we need together with those variants to figure out what we should do with those folks is going to be a big challenge.

(Slide)

Environment?

(Slide)

Coming out and again involved in the GENEVA project the Genes and Environment Initiative that started back several years ago at NIH sought to come up with better ways of measuring these myriad of potential environmental influences and I think we are now just beginning to be able to touch this.

(Slide)

There was just a paper out a week or two ago looking at common environmental differences and the potential effect

on SNP markers relevant to breast cancer and actually they did not find much on the effect side.

(Slide)

So models for moving forward; you have already heard from Dietrich the idea that you could use existing cohorts to do these studies. I think there probably is need to consider, a very much need, to consider large prospective studies moving forward. And this is from the Common Fund website talking about that.

(Slide)

I think ultimately though, it is difficult to envision how we are going to sort this information out without a concerted effort to develop the infrastructure to harness our clinical informatics systems to help in real-time doing research on whole-genome sequenced variation and what it means.

(Slide)

There are some efforts afoot to do just this, again from the genome-wide association world and also through Teri Manolio's shop, the eMERGE Network. Their paper is coming out already sort of validating that this approach works for replicating previously noted whole-genome associations with SNPS.

(Slide)

And then I think we have a whole raft of other

questions that we need to tackle. Will society act on this information in productive ways?

(Slide)

This is a press release from the last couple of weeks relating information coming out of the Multiplex Study. For those of you that are not familiar with multiplex and other NHGRI activity in the Intramural Branch with Colleen McBride, I would suggest that you go take a look at this website. Basically they set up a SNP panel, deployed it in the Henry Ford Healthcare System and looked at how patients responded to and interacted with having this type of information made available to them. And it is eye-opening, what they have come up with.

(Slide)

So I think this issue of the science and behavioral change is hugely important. Behavioral change at the level of the individual patient, behavioral change at the level of the clinician, maybe behavioral change at the level of our medical legal system.

(Slide)

So at this point in time we also have the issue of can the rubber actually meet the road in terms of our delivery systems that we have set up?

(Slide)

And this is a great paper by Maren Scheuner who

looked into this in some detail and basically our electronic health records systems are not at all prepared for genomic data. We can barely handle family history information at this point in time let alone whole-genome sequence data.

(Slide)

We would like to get to a point in the future where we can integrate clinical decision support with whole-genome sequence data with the rest of the information contained in electronic health records.

(Slide)

So yes we are at 10 years. Yes there are growing pains. I think there is tremendous progress potential moving forward. We need to work through these bumps in the road.

(Slide)

I think we need to keep our eye on utility because we are really all about the same thing whether you are a primary care clinician, a genomicist, an oncologist, or just a person out on the street; you would like to get to this point.

(Slide)

So I would like to thanks the folks who have contributed to the slides and thank you all again.

(Applause)

DR. ENG: Any clarifying questions for Greg?

(No response)

DR. ENG: All right, seeing none, Emily Edelman is

up next. Emily is a Board Certified Genetic Counselor and is currently the Project Director at NCHPEG. Emily received her Masters at BCU so this is indeed her home and we were blessed to have Emily as our genetic counselor in my institute, the clinical arm, the Center for Personalized Genetic Healthcare.

Emily is one of a handful of genetic counselors in the country that very quickly embraced genomic counseling which I made up, am I making up words, and put together a curriculum for our own counselors as well as others in the country who are interested.

So I asked Emily because remember I said practicing geneticists are rarer than astronauts. Greg talked because the primary care physician is the key for families and, guess what, genomes. And our patients, we know, read in *JCO* recently, our patients do not even understand 30 genes and Oncotype DX and that is somatic work. I doubt very much they can understand all these variations in 30,000 plus genes. So here is Emily and she will tell us all about how we educate and make our patients understand all of this.

Impact of WGS on the Practice of Healthcare

by Emily Edelman, M.S., CGC

MS. EDELMAN: Thank you Charis that is very generous and thank you for inviting me to speak here today. It is quite an honor to be included with this group of experts and it is actually quite a treat to be invited to give a talk on a

complex topic and be able to skip over all the background information because it has already been covered for me. So thank you to the speakers who spoke before me; that was excellent.

I have been asked to speak about a topic that is somewhat of a future event so therefore some of my talk is going to be a little bit speculative. As much as possible, as Charis said, I want to bring in practical examples of current genetic medicine practice that we can examine in this conversation about the impact of whole-genome sequencing on the practice of healthcare.

(Slide)

So this is just a slide that summarizes the key points that the committee has asked me to address today. How is WGS being applied to clinical practice? How will WGS change the practice of medicine? And one could also say, will WGS change the practice of medicine and if so, how?

And I am going to try to address these following points: informed consent, communication of results, approach to variants of uncertain clinical significance, and both clinician and patient and consumer education.

(Slide)

So skipping over background, which is fun, let's get into a case study. This is again somewhat of a futuristic event and we make some assumptions about the availability of

clinical utility data that we have as Greg discussed.

So here is Sara, she is 32, she is coming into her OBGYN and she has questions about breast cancer screening and family planning. Her sister's son recently was diagnosed with cystic fibrosis, her maternal Aunt had breast cancer diagnosed at 56, and her paternal grandmother was diagnosed with breast cancer at 63. So she has questions about screening for these conditions and wants to know if she and her husband have another child, will they have a child with cystic fibrosis. So the OB orders the genome.

(Slide)

In a few weeks Sara and her husband go in for follow-up. The doctor is able to log into Sara's genome portal through the laboratory or through her HER. And based on the family history, the indications for which Sara came in earlier, the OB can query, let's say in this situation "breast cancer panel" and "prenatal panel" or "preconception panel." So this query in Sara reveals that she has a heterozygous mutation in CHEK2, a heterozygous mutation in FGFR2 and she is indeed a cystic fibrosis mutation carrier. This testing also identifies that she is a carrier for three other rare autosomal recessive conditions that could impact a future pregnancy and in this scenario she had 36 variants of unknown clinical significance that were identified on the breast and prenatal panels possibly associated with disease.

So lucky for Sara and lucky for her OB, there is extensive clinical decision support that is in this reporting system that helps the OB take this genomic information, incorporate it with Sara's personal and family history, and come up with a more personalized management plan and recommendations.

(Slide)

So the OB can counsel Sara about her breast cancer risk, and in this little situation that I have made up, these data would mean that she would have a mammogram at 35; so younger than average.

The OB also discussed with the patient some of the considerations about these variants and what this would mean for Sara in the future.

The OB orders the husband's genome and simultaneously refers this couple to genetic counseling to have a conversation about the husband's results and also discuss cystic fibrosis and some of these other conditions that might impact a future pregnancy.

So this was a fun example for me to play with and come up with and we all have great imaginations and we can think about the potential even beyond what I have talked about here of how whole-genome sequencing can impact healthcare.

(Slide)

But how do we get from where we are here today to

where we need to be?

Of course we need affordable testing and that is what we are talking about here today. As many people have talked about before me, we need more information about clinical validity and utility for specific gene-disease association, specific SNP associations, and I definitely think this includes information about the ethical, legal and social implications of testing. We need data management and decision-support systems. And I have learned something here today; I think I should have said data interpretation systems and clinical decision support systems. We need someone to pay for this. We need our professional societies to recognize changing practice and provide recommendations on education for clinicians. And of course we need informed and educated consumers.

So when we look at this list of requirements, and there are many more that I have not identified here, and think about all of the things that we need as a healthcare system and as a society to put together in order to be able to effectively integrate whole-genome sequencing into clinical practice, it is clear that the affordable testing is coming first. So we have some gaps that we need to address.

(Slide)

When thinking about -- before we can even talk about informed consent and risk assessment with communication of

results, we have to ask the question of why someone would be ordering whole-genome sequencing or what would they hope to learn. And a few of the speakers before me have also talked about this. What is the motivation and will this qualitatively change patient management? Will this result in an action or behavior change?

So there are a few different models, and again I think Dr. Stephan first introduced this idea, perhaps one model would be when a clinician orders a genome and queries information about a targeted panel, part of targeted risk assessment, diagnostic, or screening for a particular condition. And this is aligned with the example that I showed earlier.

Another model could be more of a preventative health or primary care model where if an adult presents for genome testing, then the clinician could pull up a list of results that impact someone's risk for treatable or modifiable diseases and counsel them appropriately.

And then of course there is the direct-to-consumer model that we know and love that I think can overlap certainly with diagnostic or targeted treatment as well as preventative health models.

(Slide)

Informed consent and consumer education; I put these together because I think they go hand-in-hand. And someone

cannot have informed consent without being appropriately educated.

So over time as the complexity of information on consent forms for research studies or for tests increases, so does the length of that consent form and that makes sense. Studies have shown, however, that the longer the consent form the less likely it is that someone is actually going to read that form and understand that form. And this is not a unique problem to genetic testing, this is an issue across healthcare as we offer more and more complicated procedures to people but it is something that we are going to have to grapple with if we want to incorporate whole-genome testing into the clinical setting where informed consent is a part of that process.

(Slide)

So again, how someone presents for testing and the consent conversation will have a little bit to do with their motivations and why they are coming in and what that model is. I think the basic principles of risk, benefits, and limitations that we currently cover with people when they come in for informed consent for a test remain the same but there is going to be an additional layer to that. And certainly we need additional education for clinicians as well as consumers.

So current research whole-genome sequencing consenting takes between 30 to 60 minutes just for the consent process itself. And current clinical whole-genome sequencing,

at least in one model, is part of a 45 minute appointment.

These are very detailed conversations, very long consent forms and this is absolutely not sustainable in our current clinical model particularly if we are thinking that primary care providers are going to have a role in this. So we need more education for our public about whole-genome testing with an emphasis on the spectrum of possible results that you can get back and the uncertainty that might be present to someone if they elect this type of testing.

(Slide)

Before I talk about risk assessment, risk communication, and results communication, I will raise the question is whole-genome sequencing different than we already do right now in genetic medicine? And another way to ask this would be does whole-genome sequencing, or real whole-genome sequencing, ask something different of us as clinicians and as educators than what we already do or we already expect healthcare providers to do?

And we can put this question up against different domains and one would be knowledge. Do people need additional knowledge about genetics, about the basic principles of genetics, to be able to talk to people about whole-genome sequencing?

Our skill-set to manage uncertainty for ourselves and for the clinicians in the room, for our patients; this is

something that doctors and healthcare providers do all the time everyday. Is it different with whole-genome sequencing?

And again our sill-set having to do with communication, risk communication and communication of uncertainty; is there something different about whole-genome sequencing perhaps in the nature of the uncertainty and how it changes over time than other uncertainties that we already deal with in healthcare?

(Slide)

So who is going to be involved in risk communication? I do not think we know this fully. There are a number of stakeholders that I have listed here that likely will be involved to some extent. I think that genetics professionals have a really key role here particularly initially in the next few years as whole-genome sequencing becomes available on a larger clinical scale.

I think that genetics professionals also have a responsibility and a role to be involved in leading and participating in clinical research to help identify infrastructure for supporting whole-genome sequencing in a clinical setting and identifying best practices for risk communication for clients.

(Slide)

I do think that as the data interpretation systems and decision support and aid for interpretation of results

increases, and whether that is from a laboratory or from another company that is aiding in that, I think as that getters better and better the requirement for the clinician to have a high-level of genetics expertise will decrease over time.

So while I think that genetics professionals are going to be heavily involved in this initially, perhaps over time we will see a distribution of that responsibility.

(Slide)

How do we communicate results and risks? I don't have an easy answer for this so I will ask more questions. What information needs to be conveyed to someone? What is the minimal information and what is the best way to present that information? Again it comes down to communication. And we really have to ask ourselves is this something different than what we are already doing?

In what context do we have to -- should we or do we have to present risk information and results? Should it be in the context of other medical information like personal history, family history, and laboratory results, for this to be meaningful for the clinician and for the client?

And how do we address those variants of uncertain significance? We have heard some mind-blowing numbers about the number of variants that are present when someone undergoes sequencing. And in one of the papers that were included as a

recommendation for reading today, Kelly Ormond's paper, that group estimated that perhaps there will be 100 variants that warrant clinical discussion, face-to-face with a client.

So if you just spend a few minutes per variant, that is 5 hours per patient, face-to-face, not even to mention prep and follow-up time. And that is not even to mention variants of uncertain significance that need to be sorted out some way.

(Slide)

So I told you I was going to try to put this in a practical context so here we go. In 2009, as Dr. Eng said, I was working at the Cleveland Clinic with Dr. Eng and Dr. Sharp, who you will hear from in a moment, and at that time the Cleveland Clinic was offering 23andMe sequencing to physicians, free and confidentially, as an educational opportunity. And the Genomic Medicine Institute was invited to participate in that to provide pre- and post-test education.

So we provided pre-test group education sessions for interested physicians where CME credits were attached, kind of in a grand rounds format. Individuals could elect, confidentially, direct-to-consumer testing if they wanted it. And they could also elect, it was completely optional, to contact a genetic counselor for post-test education and counseling.

And so for the people who did contact me, we

scheduled or we had kind of pre-appointment appointments on the phone, which this is a little bit different than our traditional appointments, where we obtained family history on the phone, talked about the results, talked about how they were going to get me their results for my review, and did a little bit of contracting to figure out what they were coming in for, what their priorities were.

We found it was most effective to put the conversation about genomic testing and what those results could be for someone, in the context of all of the other medical information that we gather as part of a genetic counseling appointment. So we gathered information about medical history, life style, family history, did a family history risk assessment and made recommendations, and then talked about the genomic results really emphasizing the potential as well as the challenges and limitations to using those data for clinical practice in 2009.

And we did document these encounters and shared this information with the managing provider.

(Slide)

So some clear challenges to an approach like this. This is within a more traditional medical system but not so traditional that -- I was able to donate some of my time to this project, we will say, because this took a lot of time. This took significantly more time than a traditional HBOC case

that I would see in clinic with Charis.

It is a challenge to work with a direct-to-consumer testing company. They are not set up to liaise with clinicians, at least not at the time.

There is this idea that has been brought up earlier today of potentially needing to confirm results particularly if you are working with a company who says their information should not be used for medical management purposes; that is a challenge from a clinical perspective. And that would be only if we identified something that -- for example a high-penetrant BRC mutation, something that would warrant medical management, that would have medical management implications.

It is really challenging to talk to people, even highly educated physicians, about the different types of genetic testing results that you can get back from even a genome scan let along whole-genome sequencing.

And conveying concepts of different weights of heritability, different contributions to disease, different degrees of accuracy and validity within the scientific literature, that is really hard. So trying to talk to someone about a high-penetrant BRC-1 mutation that has clear medical management implications and then a low-penetrant variant that may or may not be validated that modify the risk for psoriasis; those are very different things clinically but they both might be due to one single gene change and that is a

difficult concept to communicate to people. And that is a difficult concept I think for people to take in and internalize unless you have a lot of medical or scientific background or if you are just really, really smart.

As we have talked about today, it is a challenge that right now we have very limited information about clinical validity and utility for a lot of these associations, limited tools and resources for clinicians, and there is a need for more education clearly which is in part what we were trying to do with that project.

(Slide)

Talking about healthcare professional education for one more moment; as I just said, it has been a challenge -- well we all know and we can all agree that it has been a challenge to get your average non-genetics provider very excited about incorporating genetics into their practice. Even for those single gene, highly-penetrant disorders where there are clear medical management guidelines and perhaps testing and screening as part of standard of care for that profession, this has been a challenge for us. And this group has recognized that and made recommendations to try to break down some of these barriers in the recent draft Education Report that was released.

So thinking about how challenging that has been for the past half a century, think about incorporating education

for low-penetrant variants, variants of uncertain significance, variants where one variant may have high validity or pretty good information about an association with disease and another variant with very poor, limited data about validity. And because of that, variants where the associated risk might change over time, this is going to be a big issue and this is something that I think about a lot as someone who is trying to provide genetics education.

(Slide)

How do we close the gap? I think that genetics professionals are going to be very involved both as clinicians but also as mentors, consultants, educators, and lab employees.

We need to continue to emphasize pre-clinical and continuing education. I think that laboratories and third parties, other companies and professional societies, are going to have a role not only in the creation of genetics education materials but also in making these materials available to other members and available to the people who need to receive them.

(Slide)

You all can read my conclusions. I think affordable testing is coming very soon. It is going to be affordable before we understand the importance. Genetics professionals have a heavy role in this especially initially. And I think

it is going to be extremely challenging to educate people but it is also an exciting time to be working at NCHPEG and NCHPEG and other organizations are dedicated towards improving access to genetics education. And I think we also have the potential right now to really make significant contributions to society's understanding of genetics because people are concerned about it right now and people are interested in it right now so I think we need to capitalize on the interest.

(Slide)

Very quickly I would like to acknowledge Flavia Facio, Julie Sapp from NHGRI and Julianne O'Daniel from Illumina who took some time with me to talk about various whole-genome sequencing applications that are happening right now. Thank you.

(Applause)

DR. ENG: Any questions for Emily?

DR. BILLINGS: Emily, the doctors with the 23andMe test, after the education event, how many actually declined to go further?

MS. EDELMAN: That is a fantastic question and I wish we had data on that. This was a sensitive issue because it was an employer offering genetic testing to its employees so it was completely confidential and we did not track that information although we certainly wish we could have.

DR. TEUTSCH: All right, I think we have come to the

end of the first part of this very illuminating discussion so why don't we take a 15 minute break and be back at 20 after.

(Whereupon a break was taken)

DR. TEUTSCH: Okay, let's regroup. Paul and Charis, take it away.

DR. ENG: Okay, is Rich back yet? So Rich Sharp is up and I think that from the public commentary, every other word smacked off the words ethics, legal, social, so it is my pleasure to introduce Rich who came to us from Baylor perhaps three to four years ago, time flies because we have so much fun, and he is the Director of Bioethics Research at the Cleveland Clinic. And he also started and directs a Clinical Ethics Consultation service which we are pleased to use every now and then. And this is actually his research expertise. He is expert on various --- on whole-genome sequencing, GWAS, and so on so take it away Rich.

Ethical, Legal, and Social Issues of WGS

by Richard R. Sharp, Ph.D.

DR. SHARP: Thank you Charis. I sort of cringe a little bit, the idea of smacking and ethics in the same sentence but I guess that is okay the way you used it. So thank you for the invitation. Thank you Paul as well for the invitation and it is a real privilege to be here to speak to the committee.

A lot of what I have talked about has already been

anticipated by several of the other speakers and if we could, could we get my slides up there please? Thank you.

And I guess I wanted to begin with a type of thought experiment for everyone in the room. The thought experiment is a simple one. Imagine that we had the ability to access the world's greatest clinical geneticist and had ample access to genetic counseling and primary care specialists who were prepared to help us in the interpretation of that information and to navigate the medical systems in which we live and help us to gain appropriate access based upon the findings of those results.

As we think about what we would want to consider as a genetic test, what would be on that list? If money were no object and resources were no object, what sorts of genetic tests would we be seeking today?

Personally I have a hard time answering that question with even a single one, even a single genetic test. And I find that quite remarkable that we are pushing so hard and so aggressively toward a movement to implement whole-genome sequence data into primary care when we cannot even think about single examples, or certainly not dozens of examples, of situations in which genetic information would be profoundly helpful right now in a primary care setting.

And I want you to hold that thought in mind as we go through and I make some of the comments that I am going to

make today.

(Slide)

Disclosures here; I have no financial relationships to disclose. It is quite regrettable actually for me and my family.

(Laughter)

DR. SHARP: And even more regrettable is the second of those, my lab is funded entirely by NIH money, which as we know there is a cliff I guess that is coming and I may be in even bigger trouble.

(Slide)

I am going to go very quickly through my background remarks here. We know that genomic costs are coming down; technology is expanding based upon the previous talks.

(Slide)

This target of a $3,000 genome and eventually a $1,000 genome is very soon on our horizon.

(Slide)

We know that there are people who are doing a lot of innovation with regard to this in thinking in very creative ways about how to manage this information, how to annotate whole-genome sequence data in ways that might actually be accessible and useful to clinicians.

Personally, I think the work that George Church is doing in this regard, though extraordinarily controversial in

the world of ethics, is remarkably innovative with regard to that. And ultimately we need to see projects like this that involve taking risks, that involve the administration of genomic analyses in a research environment. We need to see these types of projects done and funded more aggressively if we are ever going to get to that point where we are going to have clinical utility associated with full-genome analysis.

(Slide)

And I want to start at my formal comments with this quote from Ken Offit and I think that Ken's prediction here is very likely to come true in the not so distant future. That "health professionals are now faced with the prospect of their patients coming to the office, DNA profile in hand, asking for preventive management tailored to their specific disease risks." We are already seeing I suppose with the direct-to-consumer companies but I think what he had in mind was something that might be clinically more relevant and might involve a more extensive type of DNA analysis. And again I think we are very, very, soon going to be approaching that time.

(Slide)

So my questions that I want to explore in the talk are these here. As we approach this time in which full-sequence data is cheap enough to generate more routinely and potentially to use in a more widespread basis in the context

of patient care, are physicians ready?

What do we do with all of this data in terms of prioritizing the return of specific results?

Who is going to be charged with doing this? How are we going to do this efficiency and effectively?

And how are we going to manage some of the many uncertainties that exist here not the least of which is how to manage the fact that the data and its clinical importance is always changing? So how do we make decisions about when to revisit that data, reassess it, and perhaps re-contact patients based upon new findings?

(Slide)

So let me start with the first of those questions; the question about whether physicians are ready. So at the Cleveland Clinic we had a system-wide initiative that was meant to expand our educational efforts related to genetic testing and personal genomic testing. A part of which involved something that Emily mentioned in her talk, the direct availability of personal genomic testing to physicians at the Clinic who were interested in participating in that type of experiment as part of an employee benefit.

We also did a fair bit of assessment to determine how much physicians knew about genetic testing and clinical applications of genetic testing.

And so we ended up surveying about 150 physicians,

you can see some of the demographics listed on this slide. The important thing here is the simple point that this was a fairly diverse sample of physicians at an academic medical center, at the Cleveland Clinic.

(Slide)

And what we heard again and again was a resounding statement that they felt that they needed more education about genetics. These slides are a little bit difficult to read from the back of the room, so I will say a little bit about these. Most physicians, nearly all frankly, said that to stay current they felt that they needed to learn more about genetics. Roughly 95 percent of the physicians that we interviewed stated that. They felt that increasing their familiarity with genetics would directly benefit their patients. And they also thought that new genetic findings were changing their practice, having an impact on their practice of medicine.

We also found, when we asked them about their baseline knowledge and familiarity with different aspects of clinical genetic testing, that they reported that they did not feel like they were very well equipped to deal with questions that they were receiving on a day-to-day basis.

(Slide)

Here, the data that we are showing here is that “I am familiar with recent genetic research that affects my

patients." Again, about 1 in 4 of the physicians thought that in deed they were familiar. The majority of them thought that in fact they were not familiar with that leading-edge research.

Most of them thought that their knowledge was not sufficient to answer questions that they were receiving in clinic. They were not comfortable explaining genetic test results and felt that their formal training in genetics did not meet their needs as physicians.

Now we could have done this survey I suspect at the vast majority of academic medical centers and I suspect we are not going to get very different results.

(Slide)

And so when we asked this question, are physicians ready for a time in which whole-genome sequencing data is going to be more widely available? I think the answer is a resounding no and that answer does not differ from what we can tell that much when we compare primary care physicians against specialists in various areas.

Physicians that are in specialty areas may be familiar with a few select tests that they order somewhat more often, but by and large their overall familiarity with genetic research is fairly limited.

And so I think when we ask this question -- or when we think about this, if physicians are not well prepared to

counsel patients about currently available genetic tests and feel that their knowledge is limited there, surely we should not think that they are very well prepared to counsel patients about whole-genome sequencing data that is going to be vastly larger in terms of its scope and vastly larger in terms of the potential clinical responses that would be indicated.

That, I think, is probably the straight-forward answer to this question of are physicians ready. No, they are not ready because they do not know enough about the range of genetic information that is going to be revealed through whole-genome sequencing analysis.

But there is a deeper point here. And it is the deeper point that I want to be sure that I stress here. And that is that the response to this situation is not simply to encourage more physician education to make sure that physicians know more about genetics. I think that is obvious and that is something that has to happen.

But the appeal of personalized medicine is actually something more foundational and involves a paradigm shift of sorts. The appeal of personalized medicine lies in its potential to move us away from a mode of delivering care which is focused upon addressing symptoms as they present themselves, the sort of episodic disease management model where a patient comes into the doctor's office because she is sick and is seeking care for those particular symptoms that

brought her to the clinic that day.

What we are talking about in part when we are talking about personalized medicine, is a shift toward more proactive, preventive, ways of addressing health problems in America. And I think the bigger question is, are physicians prepared for that foundational shift, that transformation in the delivery of healthcare services? And I want to suggest that the answer to that is also no. That we do not have a healthcare system that supports physicians spending time counseling patients about disease prevention, that supports physicians being able to sit down and have an extended and comprehensive discussion of health and the things that patients can do to address their health-related needs. And that more fundamentally, lacking that infrastructure, we are always going to struggle with questions about who is going to provide this kind of information? Who is going to counsel patients about the preventive implications of genetic information?

So I want to suggest that physicians are not only limited in their current education about genetics but more basically, not well-prepared to respond to this foundational paradigm shift that we are seeing and that I think is signaled by the appeal of whole-genome sequence data.

(Slide)

The second big item that I wanted to spend a little

bit of time talking about is this question of how to pick and choose which results to return to patients if in fact we do whole-genome analyses.

So there are going to be many, many things that are going to come out of a full-genome analysis that are going to be unanticipated; unanticipated in the sense that they do not appear to be related to that particular patient's clinical presentation. Maybe it is a result that is related to an adult onset condition. Maybe it is a recessive mutation that is profoundly important in terms of reproductive decision-making. There will be lots of things that perhaps we will not be able to anticipate that are going to fall out of these types of tests.

And as a result of that, I do not think it is realistic to believe that we could sit down and counsel patients about all the different types of diseases, all the different types of genetic information that might be revealed during the course of a whole-genome analysis. And that issue I think calls into question for me the very possibility of getting something that approaches informed consent. At least informed consent as we typically understand it in the context of clinical genetic testing.

And that if we are aspiring to put patients in a position where they are going to be able to provide that informed consent, I think we are working toward something that

is unattainable. So what that means is that I think we have to readjust our standards here if we are going to be embracing the use of whole-genome sequence data in patient care. And I think we need to be comfortable with something that is not as informed in terms of patient decision-making as similar sorts of decisions might be if in fact we are evaluating single diseases or single genes. There are going to be some compromises, I would suggest, with regard to patient care and compromises with regard to informed consent in particular.

(Slide)

So we are doing a study that is looking at some of these practical challenges that are associated with whole-genome analysis. And this is a study in which we are seeking to describe both patients' and genetic professionals' attitudes and beliefs about multiplex genetic testing, genomic testing being one example of the type of testing that we have in mind, and trying to identify what clinicians believe patients should know prior to making a decision about whether this type of testing is right for them, as well as what patients would want to know before making the decision.

And ultimately our aim here is to develop some practical guidance about how to talk to patients about genomic testing and how to make these decisions about what to prioritize in returning particular diagnostic results.

This is a study that is funded, incidentally, by the

National Human Genome Research Institute.

(Slide)

So our approach here is to do a series of in-depth qualitative interviews. We are doing these initially with patients that are presenting to genetics clinics. These are patients that are often seen as being on what is called a genetic odyssey meaning that they may have been referred from one physician to another physician with the expectation that they have some genetic disorder but no one has been able to provide a definitive diagnosis as to what that disorder is. That is the type of situation in which perhaps whole-genome analysis might be clinically appropriate to order. We are interviewing these types of patients who are finding themselves amidst that genetic odyssey.

And then we are also constituting expert advisory groups of genetics professionals at leading medical centers around the country. And what we are doing is we are saying to these professionals imagine that your institution was planning to offer whole-genome analysis as part of a clinical service; imagine, that in fact, they were rolling out that type of testing at your institution. Who would you want in the room to serve as expertise advisors with regard to the structuring of that service and the communication of results? And then we are organizing these working groups based upon what our local contacts and site coordinators recommend to us.

After this qualitative interviewing, what we are going to do is we are going to do some surveys of patients for whom genetic testing might be appropriate and ultimately do some practical work trying to develop clinical practice guidelines.

(Slide)

So I am going to speak to you a little bit about the expert advisory groups. Again a part of the aim of this process is to identify what things genetic professionals would prioritize in returning information from whole-genome analysis.

So we have groups of 8-10 genetic professionals at six partner institutions. Typically in the room are multiple clinical geneticists, genetic counselors, and experts in bioinformatics or public health genetics. These advisors that we have attend a series of meetings, so this is not a quick in and out type of process here where we simply ask them for their gut feelings, we go there on several different occasions and really begin to develop a rapport with them and ask them how would you deal with this particular type of clinical context? So we are giving to them mock reports that are coming out of multiplexed arrays and asking them how would you deal with this particular type of test result and make decisions about what is important to cover and what you might wait and defer and cover in a future meeting.

And because of that, I think the information that we are getting is actually quite unusual and quite unique in addressing the practical challenges of communicating whole-genome data.

At this point we have done 18 of these different meetings. I am glad my wife is not in the room to hear that number.

(Slide)

The expert advisory group, some of the major findings coming out of our study so far, and this is still in the very early stages of data analysis because we are still planning to go back for one additional meeting, but what we are learning so far is this. That genetic professionals, and I should be a little more precise here, those genetic professionals that are considered leaders at academic medical centers that are on the leading edge of genetic medicine, do not believe that highly multiplexed forms of genetic testing are ready for routine clinical use.

So as a companion to some of the remarks that Greg was making earlier about the lack of preparation that primary care professionals may feel at this point, it does not get much better for people that are leading professionals in genetics either. They do not know what to do with this information either.

Many of them are concerned that there does not

appear to be sufficient clinical data to support the utility of multiplexed forms of genetic testing or whole-genome analysis. They worry that it will be difficult to put patients in a position to provide informed consent. And they are worried about false positives. About identifying what appears to be a mutation and then having to track down that information later on by administering things like targeted full-sequence analysis of individual regions of the genome.

(Slide)

We also found that they struggled to articulate a clinical situation in which it would be appropriate to order whole-genome testing. They struggled to say what they would consider to be the higher priorities and lower priorities in terms of clinical interactions with patients. Often times they would say that once the data is in hand and it has some clinical implications, you have to review everything. If it is relevant to patient care in some broad way even if it is a SNP association that is loosely documented, it is still something that you need to discuss with patients.

And so they had a difficult time making these decisions about what to prioritize and what to defer for another time. And part of this has to do with the culture of clinical genetics in which the approach of most clinical geneticists is very conservative with regard to the ordering of diagnostic tests. You order a test based upon a patient's

clinical presentation and you know what to do with those results afterward because you have not looked for everything at the same time.

And so what bothered them the most about whole-genome sequence data was its scope. They thought why look for everything; why not look for things that are indicated clinically. And again, why order a test if you do not know what you are going to do with the results afterward; that sort of manta of diagnostic testing that we often hear.

So the important point here is the one at the very bottom of this slide, that these are the medical professionals with perhaps the greatest experience with regard to clinical genetic testing and they are clearly urging caution with regard to clinical applications of whole-genome sequencing data.

(Slide)

So the last issue that I want to cover, I am going to skip in the interest of time, I simply want to say that with regard to genetics, we are all aware of all the misconceptions that exist about genetic information. We are worried about the possibility that patients might over-read genetic information; see it as more predictive than it in fact is. And in this situation where there are so many uncertainties and so many unknowns, I continue to think there is a great need for research examining the social implications

of genomic medicine.

(Slide)

We could all articulate a laundry list of different questions that we would consider to be important in this area. At the very top of my list though is this concern that we do not have good outcomes data related to the impact of genetic risk information on behavior. We do not know, if in fact, personal awareness of genetic risk information is actually predictive of improved health outcomes. We do not even know if it is predictive of behavior change which might be a surrogate for those long-term measures but we certainly do not have any good quality data that is long-term prospective data looking that the impact of predictive genetic tests of the sort we are talking about when we are talking about whole-genome sequencing data.

We are working with a group at Baylor to try to generate some of that information.

(Slide)

And this is where I sometimes feel like we are right now, which is that we have all these really remarkable tools that are coming from clinical genetics and we do not yet have the social infrastructure to be able to administer these tools in a way which is very effective.

(Slide)

There are lots of folks that helped with our

project. I want to be sure to acknowledge the help here from our site coordinators and the group at Baylor College of Medicine that we are partnering with on many of these studies and sorry that I ran a little long on time. Thank you.

(Applause)

DR. ENG: Jim?

DR. EVANS: That was absolutely fantastic, that was great. I just wanted to ask you how you might think about -- I completely agree with you on informed consent, and I just urge you to maybe think about or maybe you could mention how it compares with what we do in every other aspect of medicine. When we order an MRI of the brain we can find out things that were unanticipated. We can find out things that we cannot change that are devastating, et cetera. So it is really no different from any other medical specialty. It is another case, I think, of genetic exceptionalism, this idea of informed consent being needed. Do you think that is a reasonable analogy?

DR. SHARP: I do not actually. I think that --

(Laughter)

DR. EVANS: You know, I really did not like your talk actually.

(Laughter)

DR. EVANS: So why not? Why is it no different?

DR. SHARP: So I think there are several

dissimilarities. One is that if you read that MRI today and you read it in six months from now, you are probably going to have more or less the same interpretation. With regard to this type of information, if an expert in clinical genetics were to look at the same data a year later, two years later, they are going to get a different type of result and I think for me that is something that is different. I think it is also different in the sense that the information has clear relevance for other individuals in that person's family. I think that is one of the historical justifications for insisting on genetic counseling as part of that pre-test routine for many clinical tests; go ahead.

DR. EVANS: I was just going to say we have encountered that before though with infectious disease which has -- you know, infectious disease tests have clear relevance.

DR. SHARP: That is true of course. But it is the constellation of things. I think one of the reasons why we have a more extended informed consent discussion with patients around genetic testing is that we want to slow down a little bit and be clear with patients that this is not quite the same as other tests that they may have consented to in the past. That in this particular case, it is not actually driven by a clinical presentation in all likelihood, right, that it may be the case that one of the things we want to cover as part of

the informed consent process here is that we are ordering this test not because you have a particular symptom but because we want to anticipate the disease --

DR. EVANS: But that is half the testing we do in medicine already. We do not order cholesterol's typically because we think somebody has a disease.

DR. SHARP: So I actually think you are right. There is a case on each side here. Personally though I do come down on the side of saying that this is a place where if genetic exceptionalism makes sense, it makes sense in contexts like this where there is such great uncertainty.

DR. BILLINGS: Thank you Rich. Our last speaker is the Chief Scientific Office of the Los Angeles County Health Department. He is also known to us as our fearless leader and to his friends and family as Stevie Boy, Stevorino, and honey.

(Laughter)

DR. BILLINGS: He has been able to teach outcomes research to Merck and Company which I would like to hear the story of sometime. But today he is going to tell us about how we should think about the economic value of whole-genome sequencing.

Economic Value of WGS

by Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Well thanks and I am going to build on what the last few speakers have been talking about. And from

an economist's point of view, in some ways, this is really simple. As Greg told you, very few of these tests have demonstrated clinical utility and if you do not have a good measure of effectiveness, it is very hard to talk about what the cost effectiveness is.

(Slide)

In general we talk about, in clinical medicine, about economic evaluation. There are a lot of ways to do that. The most conventional way and the one that is recommended by the panel on cost effectiveness in health and medicine is a cost utility analysis which is cost per QALY which combines morbidity and mortality in a single measure. But the bottom line is it is a health outcome.

And I think it is important to note that while we are going to be talking about what might be cost effective, cost effective actually means a service that provides reasonable value. It does not mean that it is cost saving. And in fact most of what we are going to be talking about is what kinds of tests provide that reasonable value because most of the tests, when we say they are cost effective and are not cost saving, it really means that they are cost additive.

(Slide)

So this is the simple formula that I want you to work with me on during the rest of the talk. And just remember that what we are going to look at is are costs

increasing or decreasing and do the health outcomes improve or not improve? I think this is the last time you see QALYs from me at least during this presentation so you can be grateful for that.

(Slide)

And it is important to think broadly. We have heard a lot about the cost of the actual test but the cost of the actual test is just one small part of what the costs are that relate to whole-genome sequencing.

We are going to be talking primarily about direct costs which are the medical costs associated, and I will talk a little bit more about them. And there are also non-medical direct costs; these are patient costs for transportation and other kinds of things. Indirect costs which are productivity costs from loss of work or loss of other activities. And then there are intangible costs which reflect grief, pain and suffering. They are very real costs but they are hard to quantify and generally not a subject of the primary economic discussion but really important nonetheless.

(Slide)

As we go through, I am going to be talking primarily about direct medical costs which include not only the cost of the tests that we are talking about but typically costs of additional visits, hospitalizations, follow-up tests, and other kinds of treatments. And we need to look at the

aggregate of all of those and think about how they compare with and without using a genomic test.

(Slide)

I think we have heard today really about two very different basic uses of whole-genome sequencing. One is a focused clinical use where we have information that is gathered specifically for the purpose of managing a specific clinical condition. Somebody is presenting with some situation, condition, or disease for which one wants additional information. And I am going to call that focused clinical use.

Much of what we are talking about though today is what I would call screening. This is testing, reporting, and using the information in a person who otherwise is asymptomatic. And that is going to be the focal point of what I am talking about and that is of course primarily the way whole-genome sequencing could be put to use in terms of germline for those who are asymptomatic.

(Slide)

So let’s talk briefly about focused clinical use. Again the economics here under this circumstance are largely the same as for any other laboratory test and it basically asks what does the incremental information that you get from doing the test contribute to better decisions, e.g., ending a diagnostic odyssey, selecting a specific treatment, or

understanding prognosis.

There are a few variants that make whole-genome sequencing somewhat different in the sense that an economist would call this a sunk cost. Once you do it, it is done. You have already spent the money, you have already got the results, and you can use it over and over and over again. So it is different in that way than many other tests.

And that usually means that there are additional focused uses which may increase the health benefits when used appropriately but at little incremental actual testing cost.

Whereas we heard there are some issues with data storage, data handling, and the clinical data support for the actual use of the tests.

(Slide)

So when these tests are used appropriately and they provide reasonable clinical value, the issue is likely to be one of financial considerations, not really economic ones. And I am not going to go into them here but it is important to note that there are a whole variety of issues here. Who pays for that initial testing and the long-term data management and access costs? How do the costs get shared among payers for first and subsequent testing? And how are clinical decision support systems maintained? Again things that are important to think about but not generally what the economists will worry about; leave that to the finance people.

(Slide)

But what I really want to talk to you about is this problem. For almost all diseases, that which is actually clinically apparent and meaningful is just the tip of the iceberg. And for screening, we actually want to look beneath the surface and see what is going on. And by screening I really mean just those who are asymptomatic, that is, who do not present with a clinical issue or problem for which someone might approach it in a more diagnostic framework.

(Slide)

So the problem with screening, and I am going to talk about this from the perspective of someone who has been on the US Preventative Services Task Force that makes evidence-based recommendations for screening in asymptomatic populations, the problem is to figure out whether early detection does or does not lead to a better outcome.

And that there are a whole series of very real risks associated with information from screening. And I will talk about those as we go through. There is the possibility for error, there are the hazards associated with follow-up, there is the question of how much benefit there is, and how much cost is incurred. And the real challenge is to identify those specific tests which provide real clinical benefit and have minimal harm so that you have a net health benefit from doing the test and remember these are asymptomatic populations.

(Slide)

So let's look at what the six possible outcomes are of screening.

(Slide)

So the first outcome, screening test is negative but the patient has the disease or the risk for the disease. We would call that a false negative and someone might be inappropriately reassured. Think about this as the problem -- and I am going to use examples from non-genomics because I think they are clearer and not only that, but I am not a geneticist and cannot find good examples; so ignoring a new breast lump because a mammogram was normal. You are going to have decreased health benefits and you may have increased costs.

(Slide)

Screening outcome #2, the screening test is negative and the patient does not have the disease. That is a true negative. There are no health benefits since the patient did not have the disease. And although the patient is reassured that may or may not always be good. So think about knowing that you may be at lower risk for diabetes may lead to suboptimal behaviors. Certainly being told from your genetics that your relative risk of diabetes is only half of what other people are does not mean that you don't have a significant risk at the same time. So you may increase cost and

inappropriate behaviors.

(Slide)

Screening outcome #3, the screening test is positive but the patient does not have the disease. We heard a lot about this in terms of how common this is likely to be to have false positives because of the testing itself. It is subject to the risks and costs of further testing and anxiety. And think about the issue with maternal serum testing for Down syndrome. It is calibrated to label 5 percent of women abnormal. It increases the cost and may increase harms.

(Slide)

Screening outcome #4, the test is positive and the patient actually does have the disease but is not destined to suffer morbidity or mortality associated with it. So they may end up getting not only further diagnostics but may be treated unnecessarily. Think of the example of prostate cancer screening. Twenty-five percent of men in the age range for prostate cancer screening have prostate cancer but the lifetime risk of death is only 3 percent. How many of those detected by screening are treated for disease that would never have made it to the surface? This increases cost and may decrease the health benefit.

(Slide)

Outcome #5, the test is positive and the patient is destined to suffer morbidity or mortality related to the

disease. But the outcomes of treatment in the asymptomatic stage are no different from treatment after symptoms actually materialize so we simply lengthen the treatment time. So think about what morbidity we actually prevent by screening people for COPD with spirometry? No net health benefit but may increase the cost.

(Slide)

So we have a sixth outcome, the test is positive and the patient is actually destined to suffer morbidity or mortality related to the disease and treatment in the asymptomatic stage prevents complications that would develop if the treatment was not started until after the symptoms were present. Think of examples like screening for colon cancer and treating it in an asymptomatic stage and that has clearly been shown to save lives. It has a health benefit and it may save costs.

(Slide)

So for five of the six outcomes there can be no health benefits to the patient. And these five outcomes are not just costly but the patients incur the harms of screening and treatment.

For only one of the six outcomes can there actually be health benefits to the patients but no assurance that the benefits will actually exceed the harms of screening and treatment across screened populations.

So how does this tie back then to whole-genome sequencing? So let's think about how that exists.

(Slide)

The challenge is really the overwhelming number of tests that are actually being done simultaneously. So you have to consider the benefits and harms in the context of having many, many, many different observations. Inevitably you will find many positive findings and inevitably many of those concerns that come from those findings will lead to follow-up. For most of those, except for the one in six rare outcomes, the harms are likely to exceed the benefits. And the costs are likely to be substantial.

And if you look at what we recommend for a routine clinical preventative service, it is a fairly narrow set of things that actually pass the scrutiny of harms being much less than the benefits on a population basis.

(Slide)

So from a screening perspective, we generally think that screening should occur when good evidence demonstrates that the benefits of detection of a disease in an asymptomatic phase exceed the harms associated with diagnosis and treatment across the entire screened population. In other words, for the asymptomatic patients, the evidence bar that we have talked about here should be high.

(Slide)

But I think the problem is that we are actually swimming upstream against these technologies.

(Slide)

There was an article a couple of years ago which talked about weighing the costs of a CT scan looking inside the heart and the cardiologist said “it’s incumbent on the community to dispense with the need for evidence-based medicine; thousands of people are dying unnecessarily.” That is what we are up against.

(Slide)

The forces for providers to actually do things are enormously greater than the forces for them not to do them.

(Slide)

Most of us are trained in clinical medicine with a noble ambition to do good and the failure to recognize and a relatively good ability to ignore the harms.

We have a cultural expectation that medical care can only do good, not harm, and that more care is always better than less.

The public and the medical profession generally have high faith in technologies.

(Slide)

There are advocacy organizations that have substantial sway over the opinions of the public and medical profession for things like screening. There is a fear of

litigation if one does not screen and there is a related problem, a failure to detect problems.

(Slide)

Even if we look at quality measures, you can see that most of them are about things that we should do. And the PQRI quality measures include 13 specific measures that include the word "screening." Every one of them requires screening. Not one measure addresses the use of unnecessary screening services.

(Slide)

There are other forces to do. In general, things get paid for. "Every dollar spent on healthcare is a dollar of income for someone." So there is profit motive. So in the debates of healthcare reform past and present, many people thought it was immoral to pay physicians to withhold care.

(Slide)

So if whole-genome sequencing translates to unbridled use of screening, then in the process of promoting prevention we will be doing much harm and healthcare costs are likely to increase.

(Slide)

So what do we do? We need to make sure that what we end up delivering here are services that have demonstrated health benefits and provide good value that have clear clinical utility.

We need to develop financing coverage and reimbursement cost systems to cover those costs and then the systems to assure their appropriate use.

Many of these slides, I should acknowledge, come from my good colleague Mike Lefevre at the University of Missouri who tried to frame many of these things. But I really appreciate your attention and I will take a question or two if you have one.

(Applause)

DR. BILLINGS: Direct questions for the fearless leader?

DR. EVANS: Do you think that the train has left the station? Do you think that it is possible at this point to say wait a minute, implementation of whole-genome sequencing into medical care is not proven, et cetera? Do you think we can put the brakes on it and do you think we should?

DR. TEUTSCH: Well I think it depends on what you mean by brakes. I think there are some areas that we have heard of particularly in cancer genomics where there are some clear indications for some of the testing. And I think there probably are some good examples here but we need to work through -- in general use.

But we need to have good examples of where there is clinical utility and we need to make sure that we have a structure in place for the kind of issues that we talked about

earlier; that we were challenged by from AMP about the ethics and what we do, the equity issues.

I do think that we need to slow down and look very hard, because once these genies are out, they are very, very hard to get back in the bottle. And that is our general experience in technologies. That is why we evaluate the new ones because it is very hard to deal with the ones that are already out in widespread use in practice. So I think it is a cautionary tale and that is why groups that are looking at clinical utility, that are doing the evidence-based genomics work, I think are really critical.

And I think there are questions that we need to answer like what should the evidentiary standard be? What are the policies that should be put in place? What are the clinical standards? Who should be doing it? What is their training? How do we make sure that people are informed?

These are critical questions that we ask so that we are not led just by a technological imperative that we can do it but that we make sure that we actually get real value. From an economic perspective, I think there is real risk that these things are going to actually drive extraordinary costs to the healthcare system and it remains to be seen whether there really are the kind of cost savings that people are hoping can be there.

DR. BILLINGS: Can I invite all the other speakers including Steve to visit the front of the room so we can ask them in group, questions. And Muin, why don't you while they are walking up, pose another question or make a statement.

DR. KHOURY: This has been a really stimulating day and I guess I have a number of comments but I think one underlying question here is I think we all agree, I mean I have heard from all of you about sort of the present value of whole-genome sequencing not being there. That there is a trajectory for growth in this area where the kinds of data that we will get, especially on clinical validity and utility or the declining costs, that certainly will cross certain thresholds. I want to know where that threshold is.

And I want to kind of fast forward 10 years from now, 20 years from now, where we have the $30 genome as Greg mentioned or maybe $100 and having Steve Teutsch's presentation in mind, 10 years from now will we know enough? Or when do we know enough to cross that threshold between research and practice for the masses? Not for the management of individual people coming in with diagnostic conditions but you know for the whole-scale testing of people for their genome so that we can use it throughout their lifetime; so the clinical validity and utility question.

I mean what kind of processes do we need? And I

have not seen that answer by any of you. I mean you have all said we need more physician education, we need more evidence, we need that, but when do we cross that threshold for action, you know the movement from research to practice?

And a specific question to Greg because you put those two circles of evidence-based medicine and genomic medicine not intersecting. Is there any reason why should genomic medicine not be subjected to principles of evidence-based medicine? Is there some kind of underlying reason why genetics should be different or exceptional from the rest? And maybe the rest of the panel can answer.

DR. BILLINGS: See if you can answer that in a short sentence.

DR. FEERO: No, now that that is out of the way.

(Laughter)

DR. FEERO: So you know Steve's presentation was really excellent from the screening perspective but I think in terms of the issue of cost effectiveness, on the effectiveness side, we need to consider more than just the screening uses for the genomic information.

To me it would seem prudent to consider a model, this may go against what the AMP gentleman was talking about this morning, where you obtain a sequence data, do not access the Full Monte if you will at the time of obtaining that, and then access the information in a graded way as needs arise

throughout the course of clinical care. And therefore, you extract perhaps a threshold set of variants that are associated clearly with a high degree of risk for the individual right at the outset. They are sort of no-brainers that you have to tell the person about.

But then the things that are in the weeds you leave in the weeds and do not actually interpret. That person then in a life stage perhaps appropriate way begins to extract information from their genome that is useful. Or perhaps by clinical encounter, they become diagnosed with a common complex condition and there is information about pharmacogenetic variants that may be relevant to selecting therapies.

And I think that a graded approach like that might be a model that avoids some of the consequences Steve was talking about and derives over time the maximal utility of having this information.

The other advantage of that is, let's say we are talking about a 21 year old who decides they want to have whole-genome sequencing. They may not elect to know about their Alzheimer's risk until they are 35 or 40. The interpretation of their genome when they are 35 or 40 for that particular set of variants is likely to be vastly different than it is when they are 21. And they probably -- well it depends on what we find out about prevention for Alzheimer's,

right now we do not have any proven way to slow it down, but you would not want that information at 21 necessarily in the current clinical environment but you might want it 15 years from now.

DR. BILLINGS: Other questions?

DR. EVANS: What phase of the discussion are we in? Are we in questions?

DR. BILLINGS: Whatever you want; questions, comments, statements.

DR. EVANS: So this has been one of the best sessions we have had in my infinite number of years on this committee.

I actually think that there is a note of optimism that I could uncharacteristically interject here and it is based on our ignorance. I think that our ignorance may be our salvation here in the sense that as most of the speakers I think have acknowledged in one way or another, the utility of the vast majority of this information is nil. And that is a good reason why primary care physicians are not that interested in genetics. I mean they say they need to know more but much of that may be they bought our selling.

The fact that when you try to come up with a list of findings in a whole-genome sequence that would have actionable utility in the clinic, it is a pretty short list. I think that there are a few but it is a pretty short list.

And that is why I am so interested in Richard's study. Because I think the way forward is that we simply have to figure out at the 30,000 foot level which of these findings make a difference.

And then what you do is you do not need to have each genetic counselor or each physician sitting for two hours and going through the whole-genome sequence with the patient. What you have is a certain list of things that have been determined by some knowledgeable people and this would obviously be -- there would be many iterations, et cetera. And the details of how you come up with that list are important. But that is an area where the Secretary's committee can, I think, have a real influence in helping formulate a mechanism by which that list is made.

And what I would appeal to us all to do is keep evidence at the forefront because I am an unrepentant advocate of evidence-based medicine. I think it is the only way forward. And we need to demand evidence that this stuff actually does any good and is beneficial. And for those few chunks or nuggets in the genome where it does, we can find ways to implement it. Does that make sense to people?

DR. REID: It does but let me add a historical context to that because I would agree with your statement that today we know almost nothing, action, about the human genome.

But I love to draw the analogy between what we are

doing right now in genomics and what happened in medicine centuries ago. And the analogy that I like to draw is that what we are building right now is a gene microscope. And there is this wonderful analogy to the light microscope.

So the light microscope was invented in 1590 by a father and son team of opticians, the Janssen's, and it was one of the great scientific tools of its time because the history of science is the history of scientific measurement tools. Because what is the scientific method, hypothesize/test, and it is the test that enables you to determine what is right and what is wrong. And the microscope is no exception. It dramatically revolutionized many sciences. It revolutionized botany because people could see how leaves worked. It revolutionized geology because you could look at crystal structures of rocks. But there was one field of human endeavor it had no effect on and that was medicine.

Even though Robert Hooke identified a cell of a cork cell, I think it was in 1656, there was no medical result that came out of the microscope, the light microscope for 300 years.

And in the 1870s there was a second revolution in microscopy and some guys invented oil-immersion lenses and the Germans invented aniline dyes and by about 1879 was the very first time that the microscope was good enough to look inside

a cell and they discovered the bacterial cause of tuberculosis in 1882.

And there was more medical progress in the three years of the good light microscope than the 300 years of the bad light microscope.

Now fast forward, we have had bad gene microscopes now for about 50 years. And what has happened? Herceptin and Gleevec, I challenge you to name a third. Okay, there are about five actually but I cannot remember the other three. Almost nothing has happened in medicine. Geneology revolutionized, right, the whole notion of the function of the human genome revolutionized; medicine nothing. We are about to change that. Because we, collectively some of the folks on this panel and others, are shipping for the very first time the good gene microscope and turning it loose on a medical community that knows how to use measurement tools. You have to give it another 5 or 10 or 15 years --

DR. EVANS: Or 3 centuries, okay. I am very serious here. I think that what you are confusing is our tremendous expertise in technology, all right, with an assumption that that will necessarily transform the way we practice medicine. And the reality is that the practice of medicine is inherently messy and will be the rate-limiting step. So determining clinical utility is not going to be transformed simply by having better sequence data. We will still have all of these

extraordinarily difficult issues of measuring the environment, of phenotype relationships and measuring phenotypes. I do think that there -- I think your analogy is actually possibly perfect and that it may be 3 centuries before -- I am being a little overly pessimistic.

DR. REID: We did the 50 years, we know have the measurements.

DR. EVANS: My point is that the rules of clinical medicine are very different from the rules of science. And I think a great quote in Harold Varmus's recent piece about the 10th anniversary of the genome got to that. He talked a little bit about the difference between science and medicine. Medicine is messy and as we have learned over and over, that when we do not insist upon data and evidence of benefit which is not going to be bought through more technology, when we do not insist on really strong evidence of benefit, we hurt people. The stakes are much higher in medicine than they are in science.

DR. REID: But so far I would argue that the discovery methodology has been to correlate phenotype with noise and we are for the first time going to start correlating phenotype with signal and you have to call it a step forward.

DR. EVANS: It is a step forward, absolutely. I just think it is a much smaller step forward than you do.

DR. BILLINGS: I am going to take my own question

and then I will take a question from Muin. Marc do you have a question as well?

DR. WILLIAMS: Yes.

DR. BILLINGS: Okay, so let me do mine first then. I think I would pose this to either Cliff or to Martin. Last week Jay Flatley at a conference announced he thought that there were at least 100,000 individuals who had had whole-genome analyses done already.

DR. : How many?

DR. BILLINGS: 100,000, that is based on --

DR. : --- (Away from microphone)

DR. BILLINGS: That is chips, that is not sequences, it is people who had whole-genome genotypes of some sort or another. And I think there is good evidence that it is price sensitive. That if you offer these things -- maybe the Case Western example or the Cleveland Clinic example is the counter example; if you do it for free, nobody takes it if you are a doctor. But clearly if you drop the price, more people will purchase it.

So since we are talking about affordability of the genome, what is the realistic expectation about pricing over the next let’s say 5 years?

DR. REID: So the prices today of complete human genomes at research quality, not diagnostic quality, are about $10,000; that is kind of the realistic price.

I think what we will see is the technology being able to cut the price in half every year. It is not clear that that is what the market price will go to because the market price may go higher because you may -- I think Jay has probably made this point as well, I know Greg --- has made this point of Life Technologies, and that is if you look at the sort of high-end genetic tests, the Myriads and those kinds of things, they tend to be single digit thousands of dollars, $2,000-$3,000 so you may not need a $500 genome in order to make that a diagnostically valuable thing.

And in particular I think there is great consensus in the community that the first place clinically this is going to have an affect is in the cancer arena. And you know cancer drugs are very expensive and there is a whole history of up-testing* there, you know, supporting higher prices. So we are beginning to move out of a cost-based pricing into a value-based pricing model.

And so I always say, if you draw the straight line, I think we saw the chart today, you know you draw the straight line of the continued improvements of the DNA sequencing cost; in 2014 it will cost a nickel, that is not going to happen. So I think we are going to get down to -- ballpark, between $1,000-$2,000. And I think very likely we could see a pause there and that the continued drops, you know, behind the curtain technologies will not affect the pricing very much

after that. So that is kind of my speculative guess about the future of market pricing.

DR. REESE: If I can just briefly comment. Obviously we are looking forward to that price going down. We will do cancer sequencing, we will do it today. In the one alliance that we are involved in, people will pay for it today.

Clearly, we as the interpreter, we are challenged there to really deliver and really show that you can do something with the findings. And again this is an exploratory trial that we are doing so I think it is for us to really get into it, try it out, try what we can do, and it is a challenge for us from the informatics point of view.

I agree with Cliff that the value-driven is what the clinical part is and it gets back to the analysis. So how good are our systems to interpret these very complex data. So I think that some of the cost will be more and more in the analysis and the interpretation; that is my view on that.

DR. KHOURY: Okay, so I will try again since only Greg answered my question although I was addressing the whole panel.

All right, so we believe in principles of evidence-based medicine. What does that mean in practice? There are two measures; I am assuming analytic validity and the costs. I mean although it is complicated, the costs will go down,

analytic performance will be better and better, we will have more data on people, we will be able to do genotype/phenotype correlations more and these are issues of clinical validity so to speak.

But the use or no use of the genome as a tool in medicine would require additional studies of utility. Are we doing more good than harm? Or are we assuming that it is good because we have genotype/phenotype correlation studies that are being done? Are we to assume that on average the use of a genome in the general population will lead to better detection, early intervention, saving lives, without doing the harms? I mean how do we get there? And the question about that threshold between research and practice?

And if it comes to me, the genome is a great research tool and will remain a research tool for a long, long time. But it seems that the price war, so to speak, or the pressure of getting the genome to a reasonable price seems to imply with it utility. I cannot imagine -- I mean assuming the genome you can buy it for $30, analytic performance is great, and you have all these annotated databases like PharmGKB and OMIM, is that enough? When do we cross a certain threshold?

DR. TEUTSCH: Muin I think you hit the nail on the head. This is incredible technology that is going to provide lots of valuable insights that can be used from a research

perspective but on the clinical side it is the interventions that actually are the things that are critical for utility as opposed to just the diagnostic.

So you can say the diagnostics gets you so far, but then we need the technologies on top of those. And some of the technologies may be pretty simple. Maybe it will be, gee this information is actually going to make a huge difference in people's willingness to exercise or eat healthy or change other kinds of behaviors. Maybe so, but we need to show that. And we need to show that the benefits exceed the harms.

I gave you the example of being told you are at lower risk, what does that do to people? You have to show that there is a real incremental benefit. We have talked about pharmacogenomics, most of that tends to be in the cancer arena. Even things where we have had reasonable basis for optimism like anti-coagulation, the jury is still out. So the genetics is just one piece of this puzzle and we are going to need a lot more information about the technologies that come after that in terms of what gets delivered in terms of clinical interventions; the things that are actually going to make the difference.

DR. EVANS: But Muin, don't you think that, and don't you all think, that we will reach clinical utility incrementally as different genes are demonstrated to show benefit? So for example, in the one example there was

something like 32,000 pharmacogenomically potentially important variants found. The vast majority of those are not, at this point, ready for clinical utility. On the other hand, if we are talking about abacavir and tamoxifen perhaps, clopidogrel, those may reach utility. So I do think one reasonable model forward is that you, again, determine what parts of the genome make sense and you implement them as they are demonstrated with good evidence to make sense.

DR. KHOURY: Thank you Jim, but I was not asking you.

(Laughter)

DR. KHOURY: Seriously, Jim and I --

DR. EVANS: It is just like at home.

DR. KHOURY: I mean we are mixing research and practice. So I think does the genome qualify as a tool for coverage with evidence development as we go along and you know hide the vast majority of the genome information because they are worthless at this point in time and as we learn more, uncover that information. I mean for every bit of actionable data today, there are thousands if not hundreds of thousands and millions of non-actionable data and this will continue for years to come. I mean it is not going to -- just because the genome is now $30 or $50 or $100 or $1,000, shouldn’t we be investing at the same time in studies of outcomes in addition to sort of this mad dash to sequence and sequence and getting

the price further and further down so that we can have the genome in our record and then kind of rest in peace and say now we deploy it for this purpose or that purpose. Should we be doing more, mixing research and practice, and what are the right models for doing this? So Jim if you have the answer to that maybe --

DR. BILLINGS: Maybe Sam and then Gwen.

DR. ENG: Marc has been waiting for a long time.

DR. BILLINGS: Oh and Marc. Marc, let Sam go and then you will have your turn.

DR. NUSSBAUM: First of all it seems obvious that over time we are going to have greater and greater clinical utility because none of us are going to stop any of the profound research and the important research that is going on. But I want to take us into the current real-world situation and wonder if several of you could speak to this. Today companies like mine across the blues are making decisions for coverage for one out of three Americans in terms of whether these tests have utility and we mentioned the several handfuls that do.

So I have two questions. One, if we look today, let’s take breast cancer, and we look at BRCA and HER2/neu, what percent of women do you think are getting state-of-the-art treatment? So we are taking -- the science is clear, the evidence is compelling, the clinical value is proven, what

percent do you think are getting state-of-the-art care based on those tests?

And then I have a second point that I am going to make after that. But what do you think that number is, what has been studied?

DR. FEERO: From what I understand, in general, it is lower than you would like it to be. So the implementation across the spectrum, again, it probably depends a lot on the environment you are in. If you are at Cleveland Clinic where the trained folks are right at hand, it is vastly different than my environment for clinical practice. So I think the answer is lower than we would like it to be is what the available evidence suggests.

DR. NUSSBAUM: It certainly is going to be lower but what percent of women with breast cancer cared for by oncologists and I think that number is pretty high getting their care. So here we have a sophisticated group of clinicians, great science, and the number as you say is lower than you would like and I suspect it is significantly lower. And then if we start looking at clopidogrel and other drugs where the evidence is also there but are being used in millions, the second most common drug as you say. So I think we have to figure out how to, today, translate what we know to make sure it reaches clinical use more broadly.

Now the second comment is about the cost. You know,

$30 genome, $100 genome, I agree with you, today many of these tests are in the several thousands of dollars. They are being paid for; several thousand dollars for these tests. So I do not think it is a matter of cost. If you think that the average American, the cost is $9,000, $8,000 a year, some number like that, where we could all have our whole genome sequenced even at $10,000 and that will not change and we can have that as a database. So maybe one could even advocate doing that and then doing clinical outcomes research on vast populations, a very different type of research, not the controlled trials that we know. So I do not think cost and getting it down to $50 or $100 is the answer. The answer is to me, clinical utility.

So I wonder if you could speak to those issues and what we should do, the real-world setting of today, and these next few years because some incredible things are happening with health reform. That is by 2014, Medicaid will be massively expanded and that is going to impact state budgets. So many decisions need to be made real-time and based on the knowledge we have today.

DR. SHARP: So the clinical utility question keeps resurfacing here because it really is the $60 million question I think here.

There is no straight-forward answer to these questions, which is why I think we are sitting here

struggling. I think in an ideal world what we would like to see is some variant of what Jim proposed, at least personally that is what I would like to see, and that is a situation where you take those genes that we know a great deal about already based upon a decade's worth of clinical testing experience, you package them together in some multiplexed way that makes sense. So maybe it is a cardiomyopathies panel, maybe it is a developmental-delayed panel, whatever it might be, you administer that prospective, maybe you randomly assign people to receive these sorts of results and others to undergo counseling but not actually get genetic testing results directly, and you follow them out over several years. And you expect the same sorts of things to show from that study as you would for any other type of prospective cohort study.

And that I think if we are going to make any headway in convincing physicians that they need to adopt these technologies, that is the kind of data they are going to be expecting. So I do not think there is a quick answer or a quick approach; but that is the data that, in my opinion, is most directly needed. And we need that for highly targeted, I mean targeted in terms of the mutations that you would be investigating, as well as the populations that you would be using that test in. We need that type of targeted study, in my opinion, long before we have more general assessments of utility of whole-genome sequence data in a broad undefined

population.

MS. EDELMAN: I completely agree and I wanted to address this idea of the large under-recognized percent of the population who do have probably a genetic risk right now that they should have been screened for, or picked up, or treated or tested. And I do not want at all to imply that I think we should give up on our traditional mechanisms for genetics education. I think we need to continue with what we are doing. But I really think that whenever possible, we need to build support for our clinicians into the HER, into the decision support, into prompts that come up with ISD-9 codes.

You know, if a woman under 50 has an ICD-9 code for breast cancer, tell the clinician in a pretty directed way to refer for genetic testing or have that conversation with her to prompt that conversation. I think that we need to do something a little bit differently to get some of these messages across. And there is only so much that the average person can remember in their head about genetics and I think we need to provide a little more support for people and give them some point-of-care resources to pick up on these things.

DR. WILLIAMS: So a couple of different things. One is coming back to phenotyping and I am not going to talk a lot about that since I have a little bit of a chance to present something tomorrow probably on that, but again I think it is just the recognition that evidence development is going to be

held back by not understanding phenotypes well enough to really be able to do the correlations that are needed with genotyping.

In some ways the human genome project has given us a hammer problem. There are huge investments in sequencing, capital investments in sequencing machines, which now means that we have this gigantic hammer and so every problem appears to be a nail that can be solved by doing more sequencing. And clearly I think some investments in other areas would be smart.

And just to carry that one step forward, Sam's question was actually a good introduction to the phenotype issue because at our institution, our cardiologists do not do genotyping for clopidogrel, they do a platelet aggregation study. And they compared the two and they say well why should we be do genotyping if what we are really interested in is platelet aggregation, that is what is going to be meaningful for the patient. We should be doing that test because it is a closer test to what we are really interested in doing. So genotyping may not always be the solution for some of the clinical problems that we are encountering and we should be thoughtful about that.

The second thing is that we have talked about evidence and we have talked about clinical decision support and you have heard me talk about the needs for that and point-

of-care education, but I think we also have to be cognizant of the fact that those in and of themselves have been shown not to be sufficient to be able to change care. It has to do with the culture of delivery. And this is what Jim was talking about.

We are just beginning to get our hands around the science of implementation of new knowledge and we don't do a very good job of it. I mean Sam mentioned the breast care, if you look at simple things like -- so if you are in the hospital for a MI, what percentage of people leave the hospital with aspirin? You know, half. And we have known aspirin works for 50 years. There are cultural aspects of how we deliver the care in all of our various micro and meso, and macro systems all the way up that interfere with practitioners really taking knowledge and applying it to care.

And if we try and do this and just say once we have the evidence, it will be sufficient to change practice or once we have the tools in place and electronic health records, that will be sufficient to change practice, we are not going to change practice because it has to do with implementation.

This is a situation where genetic exceptionalism clearly has no relevance whatsoever. It is applicable to anything that you are trying to do in terms of moving the needle of improving care. The data is more complex. There are going to be more challenges in terms of managing the

information but the basic cultural changes with implementation remain the same.

And I think that we have to pay attention to that. We cannot just say that developing the evidence is going to be enough to make people better, it will not.

MS. DARIEN: So I have a couple of things that may or may not be related but I actually would like to build a little bit on what Sam said because I think BRCA, having a BRCA expression whether it is 1 or 2, is actually a really good example of the complexity of this because this does not necessarily lead to the state of care. It may lead to a state of screening. So you may go into a high-risk screening program as opposed to care because there are so many different options and that is where genetic counselors come in. It is also where the risk of screening comes in and some of the benefits and harms of screening because there are different things to do with those. And it has also evolved over the period of years.

And then when we are talking about herceptin, herceptin again is another really good example of how things have changed in terms of breast cancer treatment. So when herceptin was first introduced, people were being given herceptin who had very low over-expression of HER2 and it was only later as the clinical trials kept on going on that they realized that you needed to have a higher expression and the

tests were changed.

So I think that these are really good examples of how the complexity and the changing of nature of all of this -- which is something that Jim was also pointing out.

I think the other thing, and this is, you know, as an advocate who has been working on a lot of this and as a long-time cancer survivor, one of the issues has always been the research versus practice and how people understand it. So people read the newspaper, you read the *New York Times*, and you see that the genome is sequenced and what does that mean for me? And everybody wants to know what this means for them. And we do not always have the answers.

And so many meetings that I am in, we are always talking about how do we tell the story of what we have done with all of the research dollars. And this is another area where we need to be able to tell the story of what we have done with the research dollars or what the promise is. And I think the analogies are really interesting, they are very compelling, but I think that they can go many different ways. So these are just some comments.

DR. : I don't think that was really a question.

MS. DARIEN: I realize that was not a question at all. I have been sitting next to Marc a lot in these meetings. But I guess the question is how do you deal with

the complexity of the evolution of what we have been doing in genetics and clinical genetics and genome-wide association studies? And how do you tell that story, continue to get the support, and also take care of patients?

DR. ENG: Emily it sounds as if it is directed at you.

MS. EDELMAN: Well I agree, those are fantastic points and it is a good question. I think that -- I brought this up in my talk the best I could. I think the issue of how we present this information -- I think it is how we think about this information in terms of the evolution of single gene disorders, multifactorial conditions, whole-genome sequencing, and how we approach it, how we compare it to what we are doing, how it is similar or different to other areas of medicine. That attitude and that belief, I think, colors the way that we think about didactic content, didactic education. It colors the way we think about how we want to provide decision support and what messages we would need to provide. It colors how we set up research studies. And it certainly affects how we communicate to people and how we think about the best way to share this information with clinicians and consumers.

So yes, great points, and I think it is something I am very interested in studying in thinking about best practices for risk communication and thinking about the

uncertainty. I think it was Rich who kind of drew out this idea that the uncertainty that we think about with whole-genome sequencing, to me it does really seem distinct in some ways than other types of uncertainty that we see in medicine because your risk can go up, your risk can go down, your risk can disappear, these numbers -- it is a very different thing for people to understand.

MS. DARIEN: Well risk is not deterministic and I think that is one of the things that people have the most difficulty in grasping is that it is not deterministic. It indicates but there has to be another -- with cancer there has to be potentially another assault on the gene, it is not just that you have a higher risk or that something has happened or you have had one assault, you might have to have two assaults. So I think that is a really critical piece that I do not believe that people really understand.

MS. EDELMAN: And I think that we hesitate to -- you know people like Bob Green have done great research surrounding what people believe about the risk. And I think we hesitate sometimes to disabuse people of certain risks because we do not know what the other factors are so we can say things like yes, there are environmental factors, there are other genes that play a role in whether or not you are going to get this disease, but there are still so many unknowns and I think that can be a barrier sometimes to trying

to provide more effective education.

DR. ENG: Thank you so Paul, Muin, and Andrea.

DR. BILLINGS: So just as a follow-up to one of Marc's comments. What is the evidence that platelet aggregation studies are a better predictor of clodroprel than anything else?

But I also wanted to ask --

DR. WILLIAMS: Do you want an answer?

DR. BILLINGS: Yes, please.

DR. WILLIAMS: I do not know the data but our cardiology group has done an evidence-based review on that and said that that is an effective predictor of patient response. So we do practice what we preach.

DR. BILLINGS: That is good. I wanted to ask actually each member of the panel if they would -- it seems to me that one of the things that is clear about this session is that there are a lot of issues in the research agenda. As well as -- if there ever is a translational moment in the clinical delivery agenda as well; and maybe there is some research sub-questions to go in the translational pod as well.

So could you each suggest maybe the top, and hopefully you all won't say clinical utility and evidence-based medicine, but the top research question that you think remains to be addressed in this whole question of the affordable genome.

DR. FERRO: I would actually argue it is the clinical validity aspect of whole-genome sequencing in terms of figuring out what variants are truly associated with disease risk or whatever phenotype you are talking about, whether it is pharmacogenomic or whatnot. I think that is the most pressing because from that flows utility studies that need to be done.

DR. SHARP: I actually would agree with that but just to add here, I do think that this question that Muin red flagged for us is a critically important one too. And that is to identify what are the appropriate outcome measures to use in evaluating these types of new genetic technologies. I would lobby for something that would be a little bit more expansive with regard to traditional outcome measures there. So things like changes in health-related behaviors would be an example of that; whether people who undergo genetic testing feel empowered to take control over their own health, whether they regret having had that type of experience, those sorts of psychological outcomes.

I think it is that constellation of outcomes that we need to add into the mix and combine with traditional types of health research outcomes. And that would be the one thing that I guess I would add to Greg's points.

Excuse me; it would be nice if the Director of NHGRI were here to be able to hear those types of comments.

DR. GREEN: I am here.

(Laughter)

DR. SHARP: Oh, okay, how fortunate.

MS. EDELMAN: Well I completely agree, I absolutely think that clinical validity is our first step before we can really effectively look at outcomes and look at the impact of these associations. I really appreciate Rich's points about thinking about outcomes more broadly. And I will emphasize that while of course I kind of advocate for an agenda surrounding research for risk communication and education which I think is very important, I do think that looking at outcomes and looking at long-term effects not only from a medical standpoint, not only from how this changes clinician behavior, but also from the perspective of personal utility and what people do with this information over their life course is really a big priority.

DR. REID: So from a research agenda perspective, I think one of the most exciting things that affordable whole-genome sequencing enables us to do is to start the process of moving away from association studies.

So association studies are statistical studies not informed by biology. We do biology after the study to try and interpret the results but the study itself is not informed by biology. And that is an unfortunate artifact of the richness of the dataset. It is not that that was erroneously done; it

was all that was enabled to be done. And we did the best we could over this last decade and a half or so with SNP association studies and there were a few good things but not as many as we all had hoped I think.

What affordable whole-genome sequencing does is it enables us to reintroduce the biology. And as we love to say, the entire world of genomics is rediscovering genetics. And we can inform studies with genetic models. And I think the first step in that direction is being led by Eric Green at NHGRI with the Mendelian disease studies that he recently announced that they are doing. This enables us to take families who have reasonably rare genetic disease but Mendelian diseases, so high-penetrant diseases of unknown causes, and then very simply do high-quality whole-genome sequencing of maybe four individuals, two parents and two children, and be able to sequence $25,000-$30,000 genes and chase down these heterozygous recessive mutations that will enable us to say, now we understand the genetic cause of this and then we can do things like testing. And potentially you would start understanding the pathways of those to do drug targets.

So we are moving away from this sterile statistical analysis of genotype to phenotype toward the mind-boggling hard research problem of pathway and network analysis. But that is where I think we as a research community want to go

and need to go and it will take a long time to get there with the exception of a handful of these low-hanging fruit. Mendelian diseases, I think, are going to be dramatic in their impact over these next five years and I commend NHGRI for putting money there.

DR. REESE: Yes, from my point of view, I think the critical thing, and he just took it out of me, are that what we had before on the SNP panels, these were just common markers and these were markers for genetic risk and what we get now is we really get full gene sequences. And we find loss of function mutations in these genes and we know about these genes from medical evidence. So what we are getting now is we are getting a much more complete picture for first all the genes but then for the whole genome.

So in my opinion, the first applications are going to be in the rare inherited diseases. We will actually sequence genes that have been known for rare genetic diseases for 10-20 years and we will find markers in there in individuals and they actually have an effect. They are not fully Mendelian but they will have an effect. So I think that is going to be a very interesting area.

On the pharmacogenomics one, actually we have 100 genes now that we are using and we are curating from the literature. And what we are trying to do is to show that if we can -- instead of doing one test at a time, we are trying

to do these 100 tests for all these genes. Yes we will find mutations that are unknown; this will be a stop codon. What we are planning on hoping to do is then we can have follow-up studies on these individuals and see do these drugs work or do they not work if we have some of these functional markers.

I think one of the big differences is we really need to understand that we have a complete picture. And we were looking for this for a very, very long time because these SNPs they were simply not very functional. And I tell you, in the OMIM database, half of them are stop codons. So if you look at just the dbSNP and the common variants, none of them are stop codons, almost, so there is a very big difference here of the functional characterizations.

So if you ask me, I think what we really also want to have is a lot more functional validation studies on markers so we can we learn more. If we have a gene and we have a stop codon, heterozygous or homozygous, can we quickly validate that?

I know in the BRCA1 and BRCA2 there are a lot of cell assays and cell-based assays for validation studies. And I think that is what we need because -- clearly that is what the case is.

For example I will give you another clear example. If you have let’s say an OMIM allele, a stop codon in the beginning of a protein sequence, and you find in a person a

stop codon right before that. So it is pretty much in the same position in that protein. Very likely it has the same function, not always, we know that from model organisms; it is not always the case but very likely. So there is now evidence that is coming and how do we treat that? Do we wait until we have one million people sequenced and find these rare mutations? Probably we do not have the time so we need to start dealing with these unknown mutations and make inferences a little bit earlier than that. So that, I think, did not really come out.

The SNP panels today are just markers for common disease and now we are going to really understand the full gene sequence, multiple mutations in the gene, and we see a lot of them.

The way we do our ranking is we see that a person has 100 loss of function genes in his genome, so we are looking at these, does it make sense? The way we are looking at it is we then have additional tests going, for example a cholesterol panel, tested on somebody that has a mutation in the cholesterol gene. So these are, I think, the studies that we are looking for, functional studies that happen. But I do think that we will get these full gene sequences which are different than SNP panels. There is a huge difference between the two because we know from biology; we know more that these mutations have a function so that is basically my assessment.

DR. TEUTSCH: I will take a little different tact because clearly there is a lot of hard science that needs to be done; the kind that we just heard about. But we have to be prepared to use these technologies as they come out. And as we start getting utility information, I think the first question is what is the evidentiary standard? I would suggest the evidentiary standards vary a lot depending on the use. Whether you are talking about people who have serious underlying conditions who do not have alternative therapies, the bar is very different than the kind of things we are talking about in doing with screening in asymptomatic populations. So we need to have a lot more discussion about what those evidentiary standards should be. We need to have a lot more discussion about, if we get them, how do we get them out there and get them used and get them used appropriately. We need some macro-level discussions and research about what the real economic implications are.

I sort of gave you a suggestion we could do the cost effectiveness of individual tests and their use. We could do that. But this has huge consequences to the macro healthcare system. And while I give you my own personal speculations that this is not likely to be cost saving, that is all they are.

I think people do need to start looking at how does it really play out when you are talking about not only very

effective technologies but also very expensive technologies in many cases for drugs in the cancer arena that are forever smaller fragments of the population in need. We need to think about all of that in terms of then how do these things get used, how do we have the right public discourse that is going to talk about not just these technologies but all the technologies that are driving what is becoming a progressively unaffordable healthcare system.

And those are hard discussions to have but I think we need to start getting the information together so it can at least be an informed discussion.

DR. ENG: So may we ask whether Muin or Andrea has questions or addressing the panel directly because if not, then if no one else has questions with the panel we should, with Steve's permission, move onto the Committee Discussion; so either of you two addressing them directly.

DR. KHOURY: I was not going to but I came up with a reason for why I should.

DR. : Berate them again Muin.

DR. KHOURY: First I wanted to thank Paul for eliciting the sort of individual response; I mean this was very useful, this last round of perspectives.

Sometimes I am accused of being a naysayer although I went into the field of genomics with full positive force that I even managed to sell genomics to a public health agency

that is very skeptical about the use of genetics to improve population health. And I have been doing this now for 13 years and we work with all kinds of partners including State Health Departments, Janice Bach represents the great state of Michigan here and we are always scratching our head.

One is sort of when is the promise of genomics because we want to use it, they want to use it, primary care wants to use it to save lives and improve health. And you know there is always that balance between using what you know versus always going after the next thing. And whole-genome sequencing is going after the next thing. It is not using what we already know which is BRCA1 familial cholesterolemia, a whole list of genetic screening like newborn screening and so on, so there is that tension.

And when we looked at this a couple of years ago from a translational pathway perspective, I think Greg you showed the T1, T2, T3, and we tried to map out the research dollars that are going into the various phases. We even looked at the number of publications in genetics that are in various phases. Guess what, most of the genetic funding and the genetic research publications are either discovery or very early translation. There is very little going on in the T2 and beyond; I call it the “road less traveled” because once you have discovered genes, once it is at the bedside, no one really publishes on how you actually implement it. How do you

reach the healthcare systems? How do you reach the underserved? How do you reach the whole population? And here we are at the -- I mean sort of the revolution in technology that is also driving us more and more toward the new without the implementation, with very little implementation resources, going into what we already know.

So it is a philosophical thing and I know the panel members may have different opinions but I just pose this out as sort of an arrow out there to figure out what we should do now while all this research and technology is being developed and what can we do to implement what we know while the next big thing gets done.

DR. FERREIRA-GONZALEZ: I think something that we also need to recognize Muin is that we talked a lot about the cost benefit to the testing and BRCA1 was brought up over and over again. Today it costs us $3,200 to sequence the BRCA1; we are talking about $100 genome. And actually there are references laboratories today that are using next-generation sequencers for resequencing certain disorders with a large number of genes; cardiomyopathy would be one of those.

So I am just wondering that, you know, how do we have this tension between having the capability of sequencing all of this information a lot cheaper than actually the target that we keep talking about but then balance it in the use of this information to actually not cause harm or using what is

supposed to be used. Because if these technologies are moving like we have seen, and I think that we acknowledge that, that it is actually going to be cheaper to sequence the whole genome and maybe use only parts of that, we are going to miss an opportunity.

DR. WISE: Thank you. My question relates to how this whole discussion is likely to be altered by the explosion in computer-based social networking; Janssen and Spencer did not have Facebook.

And my concern is that we are acting as if we have control and that these decisions are actually going to come from our constituencies rather than from a different direction. $100 genome, people spend more money voting for American Idol than that. And what are the implications of the fact that this may be really just a co-modification of something that we take very seriously but the rest of the world may not very soon and you get a kind of participatory genomics, mass genetics going on. We see this happening in other areas, what we used to call medicine. And that in fact, we are going to completely miss the boat unless we recognize that this conversation and the challenge to clinical utility which of course is very true, but the challenge is not going to come from this discussion it is going to come from a completely different direction. And how do we both educate ourselves but also prepare the policy discussions to engage

this in an informed way?

DR. REESE: I completely agree with you. I think the price point is clear. And if you look at the direct-to-consumer companies that are out there, I think one thing we have learned is that if the price point drops, at some point many people will just go for it. They do not know what they are getting; they just do it for the fun of it.

From the experience in the industry that we are seeing is that the price point of $3,000, $1,000 is still a little bit too high. $300, people will pay for it. And $100, everybody will pay for it. And the important thing is -- and I do think this will happen and I do think that more and more people will actually participate in some of these studies. And maybe that is where we will actually do research in the future, based on these datasets.

The question is really when it is happening. And you know we talk about $30 and $100 genomes, that is not next year. To really -- fully-loaded costs to get a full genome done at a high quality, again, that is optimistically three years out but maybe even more. But I do agree that there is a big driver in that direction.

DR. WISE: Yes, I happen to teach at Stanford and there are students being offered this test.

(Laughter)

DR. WISE: Well I do have to recognize my colleague

here and respond to the snide remarks he has made through the course of the day.

But what was interesting is how quickly they decided to do this but also how shocked they were that I hesitated. That this is generational and what we are facing I think is a kind of transformation in the way people think about identity and certainly shared identity that we really have not confronted adequately in this conversation.

DR. McGRATH: I will be quick. I am going to start it at a 30,000 foot level but I promise to get down to the ground quickly. The analogy of the microscope and how technology perceives our knowledge of how to use it is exactly right, it is a great example. But I would counter a little bit that indeed it opened up, just like the telescope opened up the skies, the microscope opened up the human body to a medical gaze and we learned all sorts of things about it that we never would have learned and we think about the body differently because of it. We desacralized the body and all of that.

It certainly led to the understanding of bacteria and the cause of infectious diseases that had such an impact on global health. A lot of people considered that the low-lying fruit at that time. That we were able to develop antibiotics and with the silver bullet able to save lives. And that, just a quick history, that did a lot, this sort of

reductionist model of medicine influenced the way we think of biomedicine which has been incredibly efficacious, exploited around the world.

We have sort of hit a place now where we are seeing more chronic diseases, that that model is not working quite so well. And then Richard you are raising the issue that the sequencing might offer a paradigm shift, that maybe we will be looking at medicine differently. I don't know if it is or not or whether we are just being able to look at more reductionists bigger, larger, I am not sure we are really trying to integrate it.

So a big compliment about this fabulous panel, and I agree it has been one of the best afternoons as you have a whole range of expertise here, and I am wondering what would it be like if we had such a similar panel looking at the environment side when we keep talking about gene environment. Is there such a panel of such experts? And if we did have such a panel, would both groups be in one room? Is there enough overlap, that is the question -- I told you I would get down to the ground. Is there enough overlap to have that discussion together or is it really two separate circles?

DR. REID: I will speak, my view about the environmental elements that are going to make their way into this whole genomics conversation are just so early stage. We know so little about it. Our experiments, as bad as they have

been in genomics, they are worse in environmental factors. So I think it is going to be a very fruitful panel in 2016.

DR. GREEN: Let me answer your question from a NIH point of view. It is an absolutely appropriate question. But I would absolutely echo what Cliff said. I mean NHGRI has several partnerships in particular with the National Institute of Environmental Health Sciences and pursuing various gene environment studies, joint studies. And really the technologies for accurately capturing environmental data, while they are advancing, they are lagging behind the genomic data acquisition. And so I think this is the kind of panel -- I don't know if it is 3 years, 2 years, 5 years down, who knows. And it is not that these groups are not talking, it is that there just needs to be a little bit of a catching up. We are looking for ways to deploy both sets of technologies for new studies but we also do not want to do that prematurely if the technologies on the environmental sensing side are not quite ready. But it is absolutely something this group should probably be monitoring to see when the developments are right.

DR. ENG: Okay, there are no other questions for the panel. Let's give them a rousing round of applause. Oh, one more, sorry Charmaine.

DR. ROYAL: Well it was really just following up on our words and Eric's --

DR. ENG: So it is for us versus the panel directly.

DR. ROYAL: Okay.

DR. ENG: All right, so let's thank the panel.

(Applause)

DR. ENG: And we will pick up immediately with Charmaine.

DR. ROYAL: When Barbara started to talk I thought oh my gosh, she took my question. It is just that I wanted to go back to Cliff's comment earlier about the need for us to understand the underlying mechanisms. I mean that to me is part of the key in even understanding how to translate this information to the clinic.

And the underlying mechanism, as I was going to say, is more than the genome and it is more than -- and it depends on how we define environment. I know at NIEHS the focus has been on the physical environment. I think we really need to expand our thinking about environment to include the social environment, the cultural environment, the psychological environments. And I agree that the Mendelian disorders are a great model to help us try to understand that.

So my comment was going to be about the need to include social and behavioral scientists, you know, understanding of the underlying mechanisms of diseases particularly when you start thinking about health disparities diseases.

Committee Discussion of Next Steps

DR. TEUTSCH: I am going to turn it back over to you all because I think the next step for us is to think about where we want to go from here. We have heard a lot of issues, I think there is clearly a lot of interest, and we probably need to begin to craft a charge for ourselves as to what we want to do.

DR. BILLINGS: We are going to pass around -- Charis and I took a crack at kind of a draft charge not knowing entirely what we were going to hear today, which now needs to be inputted by everyone here.

DR. EVANS: So I would just advocate that we need to keep in mind that we need to tell the Secretary something about this, right. So we can think about and talk about all these fascinating issues but at the end of the day what we want is to tell the Secretary what she ought to do. And I have ideas about that but we need to, I think, figure out how to operationalize the integration of what makes sense into medicine and how we do that and how she can help facilitate that. I just want to make sure we do not spend all of our time thinking about this at the 80,000 foot level.

MS. WALCOFF: Jim you stole my line today.

DR. ENG: So you really cloned his statement?

MS. WALCOFF: I am usually -- I feel like I am always the one assigned to say remember we need to give the

Secretary recommendations to implement that she can implement and that will move the ball forward and to bring it down to that but that is -- I don't know if that is success or failure as we are getting closer. In space too, next thing you know we are going to be next to each other.

DR. EVANS: That must seem frightening for you.

DR. TEUTSCH: So let's talk about how we get to that point where we have something wise to say about what to do.

DR. WILLIAMS: Well, just quickly looking over the bulleted list here, I think it captures what we have heard pretty well today. But taking Jim and Sheila's comments to heart, it seems to me that the Secretary has some control over a portfolio of resources. And one of the messages that I heard loud and clear today is that it is more than just sequencing. Maybe I heard it because I said it. But it is more than just sequencing.

So I guess I would advocate if there is something that we could send from the committee to the Secretary about how we would perhaps balance a portfolio to more adequately address issues that do not relate necessarily to the technologies or just the shear generation of information but address other issues that we have heard about; the social implications, the implementation issues, the issues of annotation, of education, a lot of which relate to other reports that we have done in the past. But we really need to

have some sort of a tangible investment to say, you know, we want you to think about this.

I mean in some ways it is akin to what was done with ELC* and the genome project. You could argue that maybe it should have been the other way around, that we should have given 95 percent of the funds to the ELC* folks and 5 percent to the sequencers because we probably would be a little bit more even if we had done it that way. But be that as it may, I think that we are out of balance from my perspective. And as a consequence, we probably are looking at a chaotic roll-out that we are going to be trying to pick up the pieces from.

DR. TEUTSCH: So Marc in addition to the kinds of things that you were talking about, I think I heard a whole variety of sort of ethical informed consent kind of issues, maybe that is what you meant by social implications.

DR. WILLIAMS: I think actually I was trying to pick up on what Charmaine had said relating to putting it in the context of health disparities. So it is just more than just the issues of informed consent or communication of risk and that sort of thing. But also reflecting the fact that medical delivery is messy and will this potentially worsen disparities and what would be the implications of that. So I think it is a bit broader.

MS. DARIEN: I would just echo that because I think one of the big concerns about personalized medicine, the

advent of personalized medicine, is will it reduce disparities or increase disparities. So I think that should be addressed in an explicit manner rather than being implicit because there is a bullet point here “barriers to the equitable access to the WGS technologies” but it is not explicit it is just implicit. And so I think it comes up at every meeting where personalized medicine is discussed. It is a clear concern.

DR. TEUTSCH: I mean there are lots of dimensions to the disparities. One is the sort of access and equitable part and the other is the information base that is going to be available for some of those communities when the studies have been primarily based in Caucasian communities. There is a whole series of issues surrounding how it gets used by these different populations.

MS. DARIEN: So perhaps that bullet point has to be “identify potential disparities” and then posit potential solutions or actions that can help ensure those disparities are addressed.

MS. WALCOFF: When Gwen was talking I was looking at the next bullet down too and just going back to your remarks Steve, I think some reference to the concept of value as well, as we sort of move forward to this. Because as you said -- and I think this again implicitly references the fact that costs may in fact go up. Is that a good thing or a bad thing? And I think that depends on the perception in concept of value

over and above affordability.

DR. TEUTSCH: So the impact on healthcare systems.

DR. WILLIAMS: I had the same reaction that Jim did or that Muin did when Paul you asked all of them to articulate what would be the next steps. Because the interesting thing was is that to a person, none of the next steps really reflected sort of these big picture items. They really reflected to say this is an extremely important technology but we think application of it in say rare Mendelian diseases or this sort of thing is really the best use of this in the near term. Now again Paul's statement is right on. We may not have a choice, it may be that it is going to go forward and that is just the way it is. But it was instructive to me to listen to a group across the range I think of enthusiasm for whole-genome sequencing to still focus on the things that we can really get our hands around and that probably somehow needs to be reflected in a charge as well. I am not sure how I would articulate that but it was an interesting observation.

DR. BILLINGS: So I wanted to ask my fellow committee members, one area that was sort of interesting to me, and I have seen this occur in several other contexts, is the comparison of this technology and its growth and its investment and potential. The social networking part may be unique to the new environment. But comparing it to let's say CT scans or MRIs, sort of how that technology so rapidly

became part. And I wonder whether we need to hear from people who have studied that or know stuff about that. Obviously there were incentives there, obviously lots of information including information that you did not ask for, generated, et cetera, et cetera. So there are some analogies both in the research side and the delivery side that I think are interesting. I wonder if that is something we should follow-up on.

DR. KHOURY: Just some reflection on the bulleted list here. Having followed the work of this committee for a number of years here and asking myself the question, so what is different about WGS than what we have done so far?

I mean sprinkled throughout this conversation this afternoon was obviously the element of sort of dealing with large scale, more false positives, and technology informatics, all of these things. But you look at the list and you take away WGS and you put genetics here, it is concern about quality, analytic validity, and technologies not clinical validity and utility. So we are kind of revisiting the old grounds. I mean there is plenty of reports and work that this committee has done and I think is it a question of just the scale, the complexity, or all of the above. I think a Task Force is a good idea and you probably do not need more data to write a report. So I am sort of looking here for help from my fellow committee members here whether or not there is

something different in this list than what we have done before.

DR. TEUTSCH: Muin, let's see if I can capture at least a couple of things that we have not really talked about here. One is, of course, we have talked about there is a lot of data. But we are also talking about, with the cost of the affordable genome coming down, it changes the efficiency with which this information could potentially be used and get out there. I mean you have these sunk costs and then you can begin to use it.

I think it has the potential for really changing the dynamic of this information and how it can be used, how widely it can be used. We have not really talked a lot about it but it has a fair bit of implication that takes us out of the one at a time kind of work into mass availability of information in which case we are going to have to figure out how to use that information smartly rather than figure out what is the specific information that we have.

And there are a lot of implications that we heard about. Do you do it -- how do you access it selectively, are you withholding information; it raises a whole set of ethical and social issues that we have touched on in some other reports like the Large Population Studies but have not really dealt with fully in a clinical context.

DR. WILLIAMS: So I wanted to specifically respond

to that. Because as I was listening, a couple of people have mentioned the idea, well you know the economists would say you do it all, you hold on to it, and you just use it on an as needed basis. But you mentioned a couple of the issues that that begins to raise. But there are a whole bunch more which is who holds the information, who has access to it? That in and of itself would probably be sufficient to get a task force going for quite a long period of time.

But there is that compelling economic argument. And if that is really what is going to drive the discussion, then in some ways maybe that is where the focus should be. We will just assume that this is just going to be done for everybody because it makes economic sense, assuming the patent stuff is figured out. So then how do we actually use this information so that we really do not bankrupt the system?

MS. DARIEN: I don't think we can just assume that this is going to be used for everybody because a $100 test is a barrier to people. I mean I might go back one step and make sure that that is an assumption that we can actually make.

DR. EVANS: So I completely agree with that. I mean for my patients $100 is a lot of money. And what I think that makes us focus on is what is our role as the Secretary's committee? If this is going to be something that is going to sweep through the fairly affluent and they are going to get their whole genome sequenced, so be it. Either that is going

to happen or it is not going to happen; we cannot make any difference.

DR. WILLIAMS: Let them eat cake.

DR. EVANS: Yes, there you go. But I think our role is that we are supposed to make recommendations about what policies should be and hopefully those will have some implications for payers and will have some tangible repercussions as well. So I think, I am not saying we should ignore the idea that this will be a social movement and will very possibly sweep through things, but I do think that we have a role in trying to set the agenda for how medicine should go forward and should be practiced. Of if we don't, then what are we doing here?

DR. McGRATH: The tiny point, I think I am going to vote for going forward with it and one of the distinctions is is that not everybody went for whole-body scans and that kind of died and I think we have a lot of reasons for that. But this does feel different because of -- the reason for me, because geneology has been so popular and picked up by so many people that are not interested in medicine or their bodies but they love that technology, I think. And through social networking, like Paul has talked about, I think there will be a different uptake of this. And agreed, $100 or $1,000 is not affordable by anybody but I think this is a little different than the whole-body scan kind of movement.

DR. TEUTSCH: So I am hearing -- Sheila go ahead.

MS. WALCOFF: I just had one more comment that I think kind of ties that together. And I liked your analogy to the imaging and whole-body scans as another way of putting that forward. And that it does not just go from where it is sweeping through to clinical practice. I mean you do have those issues of regulatory oversight for commercializing it and marketing approval. And those same -- how will that be evaluated by the largest payer, CMS? And Jeff is not here so I can pick on him again for that. How will that be addressed in terms of that government oversight as well? And I think that is something that this committee can kind of help since that is moving together in a lot of our other contexts that we have discussed and I think in just general practice.

MS. DARIEN: I was not -- I mean I hope it wasn't unclear, I was not saying we should not go forward with it. Really what I was saying is that we should be explicit about how it fits in with our charge of being genetics, health, and society and what the societal implications are, not that it is not going to happen. And whole-body scans are a totally different thing. But it is -- we do have to be explicit and we do have to be mindful of what is affordable to one person is not affordable to everyone.

DR. TEUTSCH: Right, so I am hearing a whole variety of issues. I am not sure if we are talking about a discreet

project that just sort of, what we would call in this group, a letter-size kind of thing or are we talking about a very large report that would be like one of our real studies. I would be very interested in getting your feedback before we actually set up a group and charge them with beginning to work on this. And that obviously we need to refine it a bit more. But I would be interested in your thoughts as to is this a relatively short-term kind of project or are we talking about a substantial major undertaking. I heard someone say, I think it was Muin, who said haven't we done all this before; we can just write it up. Maybe we just need a stapler. I am not sure if that is right or if --

MS. WALCOFF: A stapler or a shredder?

DR. TEUTSCH: Maybe we will shred it and then put it back together. But I think what Muin is saying is that we could extract a lot of this from previous reports and recommendations and assemble it. And then others -- I think there is the question of how much new is there here that is going to take some more background kind of work.

DR. WILLLIAMS: And I think that comes back to the fundamental question that Jim and Sheila raised which is what are we really wanting to tell the Secretary? And I don't have a clear picture in my head about what we are trying to communicate. I mean I have suggested some things that we could potentially tell the Secretary but that seems

fundamental to decide do we really have anything to say to the Secretary and that in some ways would then, depending on what it is we want to say, would determine whether it is going to be a relatively succinct letter versus a major report.

DR. TEUTSCH: Well let me ask Charis -- Eric you are raising your hand so go ahead.

DR. GREEN: So I am an ad hoc member so I do not have official business necessarily except just to give opinions. But one observation I would make is that the field is moving faster than a committee like this can deal with. So 4 months or 6 months with what is currently happening is a huge amount of time.

So without necessarily knowing exactly what you might produce, I might suggest that you at least put into motion enough of a framework for trying to catch the issues that you can even identify now, recognizing that they will be even far more advanced by the time that you actually catch those issues and you will have other ones. Whereas if you do nothing, I think you will really struggle to catch up.

There are already several suggestions of what you might want to do just to keep trying to get assimilated and I can guarantee you by you becoming assimilated in today's issues, the ones 6 and 9 months from now will even be more striking. So without maybe trying to define too precisely the product, just if you had a framework for regularly, or semi-

regularly, updating yourself and trying to hold on to this fast moving train, I think the committee would be in a better position to say something in an informed way.

DR. TEUTSCH: So if you were advising us as to the key issues that you think we can grapple with over, what I am hearing as the short-term, what would those be?

DR. GREEN: Well we heard several of them. I mean I think -- I mean clearly to start with the shear dealing with the massive amounts of data, we are struggling with at a basic science level. But we heard lots of discussion here that even once you get your hands around that, clinical utility, I mean all these issues as it enters the complexities of the medical care system. You know I heard a suggestion which I think is an interesting one which is to look for analogies where this has come in, where a technology wave such as whole-body scanning and so forth, I think there might be some lessons to be learned there.

I am actually not sure, I do not want to insult anybody, but there is a whole field out there of individuals who are medical bioinformaticians. Medical informaticians who are really trying to get positioned to where the electronic medical records are sort of intersecting with all this genomic data and thinking about how it is really going to be put into an information system that physicians might be needing to deal with. We heard a little bit about that today; I don’t think

we heard as much as what is out there; so maybe learning a little bit from them. I could probably think of some other things but it just seems to me that if several people thought about it, this wets your appetite, but I think there are a number of additional things that you could quickly think of that you would probably love to get updated about in 4 or 6 months.

And maybe table the idea of what the product is going to look like. And every 4 to 6 months, getting a little bit updated on what is going on technologically, would be well within your interest because it is happening fast and furious.

DR. TEUTSCH: So you are suggesting sort of an on-going task force.

DR. GREEN: Well I am just thinking out load here but I hate to see you try to over-define now what your product should be.

DR. TEUTSCH: I do not think we are going to do that today.

DR. GREEN: But maybe an ongoing working group or task force, whatever the right word is.

DR. FERREIRA-GONZALEZ: I suggest we establish an on-going working group to get a recent product that goes back to the Secretary; because if we do not deliver anything to the Secretary, we can continue to discuss.

DR. TEUTSCH: Right but we can have a series of

things depending on --

DR. FERREIRA-GONZALEZ: I think also one of the issues that I think are very important are not only according to clinical utility and ethical issues, but from the practical point of view, you know, lack of standardization of the data, has come to the instruments of how we are actually going to put into interchangeable, interpretable electronic health records. Those are the key issues that we can tell the Secretary, you know, and convene a group and develop some of these issues.

Also try to develop an effective approach to the question on the multi-disciplinary research agenda. And maybe also developing databases and where all this information is starting to be housed. And somebody can actually query and try to get to the clinical validity and even clinical utility of these data.

So as we continue with the working group, maybe we can have several products that have come out, maybe letters to the Secretary, to tell her how the issues that we have addressed. And as this moving target moves, just continue to keep her abreast of what are the new issues that are coming out.

DR. TEUTSCH: So I think there are a lot of ideas on the table and the hour is getting late. What I suggest is we go ahead and form a task force. I think they can take these

ideas, begin to work with them. I think this is a topic we may want to revisit in October and with a clear sense of more focus either on some short-term kinds of things that we can do as well as some longer ones. Because some of these, I am hearing some longer term social, ethical kinds of issues that are not in the same category.

But if you all are amenable to that, what I would like to suggest is the folks who put together this great panel, Charis and Paul, we can charge them with the leadership of this group and ask for some volunteers. Paul and Charis are you willing -- you are smiling so I guess it is okay. And see if we can get some additional members to work with them; Jim, Andrea, Muin, Janice, and Charmaine; others? Okay, those of you who did not raise your hand are not spared so we may come back.

DR. WILLIAMS: I am not raising my hand but I think Eric's point was well taken. I would suggest that you look for an outside member of that group that has bioinformatics experience because as we have heard here a number of times, our current electronic health record environment is not capable of handling even simple genetic tests much less what we are talking about. And so I think it would be -- and so someone like a Mark Hoffman at Cerner who has had a lot of emphasis in this space, that sort of thing.

DR. TEUTSCH: Mark Hoffman came and spoke to us last

time. Eric do you have some specific suggestions?

DR. GREEN: There are some people at Vanderbilt. I mean Vanderbilt --

DR. : Eric --- would be one of them.

DR. GREEN: There are several names there and they are right in the thick of the storm in doing some very creative things.

DR. TEUTSCH: We may get back to you with some others. We can certainly get other *ex officios* and ad hoc members so that will be great.

So we will start with that group. Thank you all and thank you for a stimulating afternoon. We are going to start tomorrow at 8:00 a.m., a half hour earlier than today.

(Whereupon the meeting was adjourned at 5:32 p.m.)