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 DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
 MEDICAL DEVICES ADVISORY COMMITTEE

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MOLECULAR AND CLINICAL GENETICS PANEL

+ + +

March 8, 2011  
 8:00 a.m.

Holiday Inn  
 Gaithersburg, Maryland

PANEL MEMBERS:

JOHN R. WATERSON, M.D., Ph.D.	Panel Chair
MARY B. MAHOWALD, Ph.D.	Voting Member
IRA M. LUBIN, Ph.D.	Voting Member
COLLEEN M. GALLAGHER, Ph.D.	Voting Member
JOANN A. BOUGHMAN, Ph.D.	Temporary Non-Voting Member
RALPH D'AGOSTINO, SR., Ph.D.	Temporary Non-Voting Member
JEFF GREGG, M.D.	Temporary Non-Voting Member
ROCHELLE HIRSCHHORN, M.D.	Temporary Non-Voting Member
STEVEN M. HERSCH, M.D., Ph.D.	Temporary Non-Voting Member
CHARLES LEE, M.D.	Temporary Non-Voting Member
STEVEN LIPKIN, M.D., Ph.D.	Temporary Non-Voting Member
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ROBERT SHAMBUREK, M.D.	Temporary Non-Voting Member
GREGORY J. TSONGALIS, Ph.D.	Temporary Non-Voting Member
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ASHLEY GOULD  
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MEETING

(8:00 a.m.)

DR. WATERSON: I'm John Waterson, and I'm the Chair of the Committee. I'd like to call the meeting to order.

As I mentioned, I'm Dr. John Waterson, and I am a pediatric geneticist. I'm from Children's Hospital in Oakland.

At this meeting, the Committee will discuss and make recommendations on scientific issues concerning direct-to-consumer genetic tests, DTC, that make medical claims.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and affiliation. And we'll start over there with Ms. House.

MS. HOUSE: Hi, my name is Tiffany House, and I'm serving as the Patient Representative. I've been serving as a patient representative since 2006.

DR. DAVIS: Good morning. Margaret Davis. I am an attorney and an educator and an administrator.

DR. HEJAZI: Good morning. This is Shahram Hejazi. I'm the Industry Representative with BioAdvance in Philadelphia.

DR. MORIDANI: Good morning. This is Majid Moridani. I'm a faculty at Texas Tech. I'm also board certified in clinical chemistry, and I do

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research in pharmaceutical and diagnostics.

DR. LIPKIN: Steve Lipkin, and I'm an Associate Professor at Weill Cornell Medical College and New York Presbyterian Hospital. I'm a clinical geneticist who runs an adult genetics clinic, and I also have a lab that performs mechanistic studies.

DR. HIRSCHHORN: My name is Dr. Rochelle Hirschhorn. I'm an Emeritus Professor of Medicine, Cell Biology and Pediatrics, and research professor. My expertise is in genetics and immunology, and I have been involved in the particular area of genetic testing as well as in cloning and molecular biology, et cetera, for many years.

DR. D'AGOSTINO: Ralph D'Agostino, a biostatistician from Boston University and the Framingham Heart Study.

DR. BOUGHMAN: Dr. Jo Boughman, a medical geneticist, board certified but trained as a statistical geneticist. I'm currently the Executive Vice President of the American Society of Human Genetics. I sit with our board and watch them vote on our policy decisions.

DR. LUBIN: I'm Ira Lubin, boarded in clinical molecular genetics. I'm team lead for genetics in a division at Laboratory Science and Standards at the Centers for Disease Control and Prevention.

DR. LEE: Charles Lee. I'm a board-certified cytogeneticist at Brigham Women's Hospital, and Associate Professor of Pathology at Harvard Medical School.

MR. SWINK: I'm James Swink, the Designated Federal Officer for this Panel.

DR. NETTO: I'm George Netto. I'm an Associate Professor of Pathology, Urology and Oncology at the Johns Hopkins University. I'm board certified in molecular diagnostics and atomic pathology and clinical pathology. I'm the Director of Surgical Pathology and Molecular Diagnostics.

DR. NG: I'm Valerie Ng. I'm Emeritus Professor of Laboratory Medicine from the University of California, San Francisco, currently lab director at Alameda County Medical Center.

DR. GREGG: Hi, I'm Jeff Gregg. I'm from the University of California, Davis, Department of Pathology and Laboratory Medicine, and I'm the Director of Molecular Diagnostics, and I have a research lab that does genomics research.

DR. GALLAGHER: Colleen Gallagher, and I am the Chief and Executive Director of the Section of Integrated Ethics at MD Anderson Cancer Center.

DR. TSONGALIS: Good morning. I'm Greg Tsongalis, Professor of Pathology from the Dartmouth Medical School and the Director of Molecular Pathology at the Dartmouth-Hitchcock Medical Center.

DR. HERSCH: I'm Steven Hersch. I'm a Professor of Neurology at Harvard Medical School and Massachusetts General Hospital. I do laboratory and clinical research related to Huntington's disease.

DR. MAHOWALD: I'm Mary Mahowald. I'm Professor Emeritus at the University of Chicago. I've worked in bioethics, medical ethics, focusing on genetics for many years.

DR. RANSOHOFF: I'm David Ransohoff, an internist and a clinical epidemiologist from the University of North Carolina, interested in the methodology for evaluating diagnostic tests and methods for making guidelines for practice.

DR. SHAMBUREK: I'm Dr. Robert Shamburek. I'm with the intramural program of the National Heart, Lung and Blood Institute. I run the lipid clinic, and my interest is in rare lipid genetic disorders and metabolism that it's related to.

DR. WYNE: Kittie Wyne. I'm an endocrinologist with the Diabetes Research Center at the Methodist Hospital Research Institute in Houston, Texas. We're affiliated with Weill Cornell Medical College.

DR. GUTIERREZ: I'm Dr. Gutierrez. I'm the Office Director for the Office of In Vitro Diagnostics in the Center of Devices and Radiological Health, the FDA.

DR. WATERSON: Thank you very much.

Just a reminder. If you have not already done so, please sign the attendance sheets that are on the tables by the door.

Mr. Swink, the Designated Federal Officer for the Molecular and Clinical Genetics Device Panel, will make some introductory remarks.

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Mr. Swink.

MR. SWINK: Good morning, everyone.

I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to

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special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on scientific issues concerning direct-to-consumer genetic tests that make medical claims. The scientific issues to be discussed include:

(1) The risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician (in other words, without a prescription). The discussion will include consideration of the benefits and risks of direct access for different tests or categories of tests that would support differences in the regulatory approach. The clinical genetic test categories that have been proposed to be offered directly to consumers include:

(a) Genetic carrier screening for hereditary diseases (for

example, cystic fibrosis carrier screening);

(b) Genetic tests to predict for future development of disease in currently healthy persons (this includes tests to predict risk of developing breast or ovarian cancer); and

(c) Genetic tests for treatment response prediction (an example of this is a test to predict whether an individual will respond to a specific drug or not).

(2) The risk of possible mitigations for incorrect, miscommunicated, or misunderstood test results for clinical genetic tests that might be beneficial if offered through direct access testing.

(3) The level and type of scientific evidence appropriate for supporting direct-to-consumer genetic testing claims, including whether it should be different than that required to support similar claims for prescription use in clinical genetic tests.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcripts.

Shahram Hejazi is serving as the Industry Representative, acting on behalf of all related industry, and is employed by BioAdvance.

We would like to remind members and consultants that if the

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discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

For the duration of the Molecular and Clinical Genetics Devices Panel meeting on March 8th and 9th, 2011, Ms. Tiffany House, Dr. Steven Hersch, and Dr. Rochelle Hirschhorn, and Dr. Kathleen Wyne have been appointed as Temporary Non-Voting Members.

For the record, Ms. House serves as a member and Drs. Hirschhorn and Wyne serve as consultants to the Endocrinologic and Metabolic Drugs Advisory Committee for the Center of Drug Evaluation and Research. Dr. Hersch is a consultant to the Peripheral and Central Nervous System Advisory Committee of CDER. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This appointment has been authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on February 28th, 2011.

Before I turn the meeting back over to Dr. Waterson, I'd like to

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make a few general announcements.

The transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Their telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area around the speaker's podium.

The press contact for today's meeting is Erica Jefferson. There she is right there.

I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration desk.

And, finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

DR. WATERSON: Thank you. Just a reminder to everybody to remember to turn on and off your microphones when you want to speak.

We will now hear the history and landscape of DTC genetic tests that will be presented by Dr. Elizabeth Mansfield, Director of the

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Personalized Medicine Staff in the Office of In Vitro Diagnostics at the FDA. At the conclusion of this presentation, there will be time for questions from the Panel members. At this time we will hear Dr. Mansfield.

DR. MANSFIELD: Thank you very much, Dr. Waterson. Good morning, and thank you very much to the Panel and the audience who have assembled today for this very important meeting.

I'm going to begin the meeting with what may appear to be an existentialist question: Why are we here? However, I hope my remarks will make it less existential as I go on.

I'm going to start with a brief history of direct-to-consumer testing to provide you perspective on what has gone on in the past, and I will follow with a description of what we see at FDA as the current landscape of direct-to-consumer genetic testing.

Please note that the history I provide is not exhaustive and does not deal extensively with individual state requirements for direct-to-consumer testing.

I would also like to give a short definition of how we are determining what direct-to-consumer genetic testing is, that is, those tests that may be ordered directly by an individual without a prescription and for which the results are received by the same individual without the help of a physician.

So History, part 1. Up until about 2006 we saw several

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companies who were offering nutrigenetic testing and other genetic testing, limited amounts, primarily through online advertising and ordering. These companies claim to offer personal genetic testing to generate genetic profiles. Based on the information provided by the consumer regarding his or her lifestyle, and supposedly in combination with the genetic profile, the companies made recommendations for changes in lifestyle, and most importantly, most of them made recommendations for nutritional supplements that they also offered.

Prior to a July 2006 hearing before the Senate Special Committee on Aging, the Government Accountability Office, the GAO, investigated four of these companies and concluded that the claims made were generally medically unproven and ambiguous and in general were misleading to consumers. This information was provided to the Senate committee and to the public in the GAO report entitled "Nutrigenetic Testing: Tests Purchased from Four Websites Mislead Consumers." And there is a web link on my slide.

As a result of ongoing concerns about these tests from several federal agencies, in a directive from the Senate committee, the FTC, the FDA, and the CDC published a statement warning consumers to approach such tests with a healthy dose of skepticism. To our knowledge, none of the nutrigenetic companies involved in the 2006 report remain on the market.

Starting in about 2007, several new companies launched direct-

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to-consumer genetic testing services, generally avoiding nutrigenetic claims. These companies primarily leverage newer technologies that allow a large amount of genetic information to be generated from a single test using technology such as microarrays.

The genetic information provided to the consumer at that time often consisted of nonmedical information such as ancestry, or entertainment claims such as hair color, eye color, and so on, generally with a small number, if any, clinically oriented claims. The companies offering the tests claim the results they provided were for informational and for educational use only and were not diagnostic in nature.

For some such companies, the genetic testing and test interpretation activities were carried out in different facilities. Most of the interpreting of test reports appeared to come from facilities that did not hold a CLIA license and were not certified by the State of California. Indeed, California issued 13 cease and desist letters to direct-to-consumer offerors, stating that genetic tests were not exempt from the California law requiring a doctor's prescription for testing and that the tests offered were not appropriately certified by the state. New York State also demanded that direct-to-consumer testing not be offered for those specimens originating in the State of New York.

In 2009, reflecting what's increasing concern over the growth of medical claims being made for direct-to-consumer genetic tests, FDA

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began informal meetings with several direct-to-consumer companies following our release of "It has come to our attention" letters to such companies.

These companies were concerned over possible regulatory implications of their business models, but claim that their products were not medical devices. Even if they were to be considered medical devices, the companies claim that the tests offered were laboratory developed tests, or LDTs, that are typically offered under FDA's general practice of enforcement discretion towards this type of test.

As 2009 progressed, FDA identified more and more companies offering one or more tests directly to consumers. These had a wide variety of claims encompassing a wide variety of risks.

In May of 2010, media reports announced a deal between Pathway Genomics and Walgreens in which consumers would be able to purchase direct-to-consumer genetic testing at Walgreens. This model included the consumer obtaining the sample kit at Walgreens, together with the test order that would be sent with the sample to Pathway for testing. FDA, upon learning of these plans, determined that the over-the-counter offering, in particular, the sale of the collection kit, was violative of FDA regulations and that the test as a whole clearly met the definition of a medical device.

FDA immediately sent Pathway an "It has come to our

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attention" letter informing the company of our determination and requesting a response. FDA met with Pathway and, through direct discussion with them, solidified its opinion that this test and others like it pose new types of risks and regulatory questions that were inconsistent with the exercise of enforcement discretion.

Concluding that direct-to-consumer testing was not appropriate for enforcement discretion, FDA prepared and sent "It has come to our attention" letters to all direct-to-consumer genetic testing companies that it could identify at that time. FDA met with each company to which it had sent a letter, to learn more about the company's business model and testing strategy and to convey its opinion that FDA oversight would be required for direct-to-consumer genetic testing.

Companies were made aware that they should prepare a plan to comply with FDA regulations or to abandon the direct-to-consumer model. Many of the companies that FDA contacted decided to exit the market, while others agreed to generate plans to come into compliance with FDA regulations.

2010 was a busy year, so there's more. In July of 2010, the GAO again presented a new report to the House Energy and Commerce Subcommittee on Oversight and Investigations in which it claimed that amongst several direct-to-consumer testing companies investigated, there were serious issues of inconsistent results between different companies,

violations of patient privacy, and misleading interpretations made to consumers.

FDA was briefed generally on the report prior to the congressional testimony but was not aware of the exact nature of the investigation or the specific findings prior to the hearing. Nevertheless, CDRH Center Director Jeff Shuren provided testimony to the committee, commenting that FDA should have acted sooner to regulate direct-to-consumer genetic testing. He also stated that FDA was working towards a reasonable and fair approach to regulation of these devices, and that is a process which continues with today's meeting.

Finally, the Secretary's Advisory Committee on Genetics, Health and Society published a final report on direct-to-consumer testing, which was sent to Secretary Leavitt at the time, calling for FDA oversight or a role for FDA oversight for these types of tests.

Today, as you're all aware, direct-to-consumer genetic testing remains as a business model, although there are widely varying opinions about the possible harms and benefits of the model. FDA, through analysis of comments to its July 2010 oversight of laboratory developed tests meeting, through monitoring of web and print media, and through direct communications from stakeholders, has identified several general themes regarding direct-to-consumer genetic testing.

Some individuals and groups have taken the position that

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direct-to-consumer testing should be limited or banned due to likely inability of consumers to act appropriately on certain information supplied by tests and the possibility of misdirected self-care. Others have championed direct-to-consumer testing with no regulatory intervention as empowering patients to take charge of their own health. Yet others, including FDA, believe that there is a place for direct-to-consumer genetic testing, that appropriate oversight should be applied to ensure that individuals are protected from low-quality testing, overly ambitious clinical interpretation, and breach of privacy that could occur if genetic information is not carefully handled.

Therefore, FDA is now working with several direct-to-consumer genetic testing companies so that they can come into compliance with the FDA medical device regulations. You will not be surprised to hear that this has been a challenge, not only for the companies involved but for FDA as well, as we work to create a reasonable and fair path forward.

As we gather here today, I can report that the number of companies in the direct-to-consumer genetic testing field has likely narrowed, in part due to FDA's commitment to apply oversight. But even as we speak, technological advances, primarily in the form of affordable whole genome sequencing, are increasing the amount of information that can be generated from a single human sample by orders of magnitude. At the same time, new scientific studies are published daily, providing new associations of genetics with disease.

FDA is exquisitely aware of the challenges these will bring to test analytical and clinical validation and to regulation in general and is actively exploring mechanisms to streamline validation where possible and to manage ever-increasing amounts of information generated by the basic science research enterprise.

I would like to make some general points about direct-to-consumer testing that should help inform discussion today. These are background and represent the variety of tests and testing conditions in the direct-to-consumer landscape.

First, although many direct-to-consumer offerings are large collections of different genetic tests performed in a multiplex manner, many direct-to-consumer genetic tests are offered for just one claim, for example, for Alzheimer's, for future of development of Alzheimer's, for carrier testing of cystic fibrosis, and so on. Some nutrigenomic direct-to-consumer tests are still offered. These are not the ones previously criticized by the GAO.

And, finally, we see a much greater interest by companies offering these tests, in those tests that have medical claims ranging over various diseases and conditions, including risks for development of future disease.

Among those genetic tests that are now available as direct-to-consumer tests, there are two categories. There are tests that generally do not meet the definition of a medical device, and these include most ancestry

tests, tests used in law enforcement, and tests that provide information that has no medical implications. There may be applications of some of these tests that could meet the device definition under certain circumstances, but in general they will not meet that definition and we will not discuss it today.

The other category is tests that do meet the definition of a medical device. These include pharmacogenetic tests or profiles, tests for Mendelian disease mutations or markers, and tests that predict future development of diseases or conditions, and there are many others.

There have been, as I'm sure you are all well aware, significant advances in technology and scientific advances that are making much of direct-to-consumer genetic testing possible. These changes present challenges in validation and oversight of direct-to-consumer tests.

Whole genome sequencing, in which the entire human genome can be sequenced at a reasonable cost in a reasonable amount of time, has become widely available and is clearly of interest in direct-to-consumer genetic testing as well as in clinical testing overall. The current whole genome sequencing platforms are still evolving rapidly, and their analytical or measurement performance is not well known. To date, no whole genome sequencing platforms have been cleared or approved by FDA.

Genome-wide association studies and other genomic studies that are now possible to perform using current technology are uncovering possible new gene-disease associations rapidly. These findings are published

rapidly and widely, and some findings have been replicated in independent populations, while some have not.

Finally, our general understanding of gene-disease association is growing. But especially in the case of common diseases such as diabetes and cardiovascular disease, there are to date no definitive findings that explain the majority of disease risk. Thus, there are considerable challenges in oversight in the use of genetic information in general that are complicated to some degree by the direct-to-consumer genetic testing model.

Regardless of who orders the test, it is still essential to FDA's mission to provide assurances that the test measurements are correct and that the clinical claims made are valid. Misleading or false information is beneficial to no one.

In addition, the regulatory apparatus must keep pace with rapidly advancing technology and scientific knowledge, as discussed on the previous slide. We must be able to assess new technologies and promote high-quality innovation, while protecting patients.

Finally, as has been the topic of many discussions in publications, the healthcare community is in dire need of training to use the new genetic information properly in a way that benefits patients. This community must be able to grasp a wide variety of genetic information and judge where it may lie on the spectrum of clinical usefulness. FDA can have some role in ensuring that clinically significant information is provided, but

healthcare providers must understand how to use it.

So returning to the non-existential question of "Why are we here?" we are here as FDA to hear discussions and perspectives on several topics, as mentioned by James Swink, from our Panel of experts, from a number of invited speakers, and from public commenters. We hope to have vigorous discussion of some of the difficult issues we have encountered in the oversight of direct-to-consumer genetic testing. We also hope to benefit from consideration of those approaches to new technology and science that are discussed by the Panel. Although this is not a voting panel, we will be listening very closely to your opinions.

Finally and ultimately, we hope to enable the public to receive improved benefit from appropriate oversight as scientific discoveries are translated into clinical care.

Although James Swink already read this, I will remind you, the three main questions that this Panel will address are as follows:

We would like you to discuss the risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician.

We would like you to discuss the risks of and possible mitigations for incorrect, miscommunicated, or misunderstood test results for clinical genetic tests that might be beneficial if offered through direct access testing.

And, finally, we would like you to discuss the level and type of scientific evidence appropriate for supporting direct-to-consumer genetic testing claims.

This concludes my talk. Thank you very much for your attention.

DR. WATERSON: Thank you very much, Dr. Mansfield.

Does anybody on the Panel have any questions for her?

(No response.)

DR. WATERSON: Thank you very much.

DR. MANSFIELD: Thank you.

DR. WATERSON: Wait a minute, we do have a question.

Dr. Mahowald.

DR. MAHOWALD: I guess my question would relate to the definition of consumer that you gave, that I think I understood, and my concern is that, as you defined it, the consumer would be the person who requested the test but, it strikes me, not necessarily the person whose genetic material is obtained and sent to the company. The consumer, as I understand it, is in fact the customer of the company, and it seems to me that the definition of direct to consumer seems to blur that distinction, and to my mind, it's a very important point.

DR. MANSFIELD: Yes. So, in general, it is not considered good practice and may be illegal to elicit or, without another person's knowledge,

send their DNA for testing. So, in general, we expect the consumer to be the same person that is tested, although that may not always be true.

DR. MAHOWALD: That expectation is not verifiable, as far as I understand it.

DR. MANSFIELD: In many cases it probably is not.

DR. WATERSON: Any other questions?

DR. LIPKIN: I have a question. She's asking defining consumer. I have a question defining actually genetic test. So, for example, there's some tests they would obviously be doing. I think of nucleic acid tests, DNA and RNA. Those are taken as a given. There are some tests that, for example, look at proteins which could be consistent with a mutation of a particular gene. For example, this comes up in the cancer genetics field. So are like protein tests then considered also genetic tests, or is this limited to nucleic acids?

DR. MANSFIELD: In general, we've limited this to nucleic acids, although it is true that you could broaden that definition.

DR. WATERSON: Thank you very much, Dr. Lipkin. Please state your name when you ask a question.

DR. D'AGOSTINO: Ralph D'Agostino. We'll probably see this along the way, but in reading materials and also hearing your presentation, I'm not clear how massive the problem is in the sense of are there a lot of companies running around it on coming to the FDA or the FDA have a handle

on it in trying to figure out how to deal with them? What are the ethical issues?

DR. MANSFIELD: Right. So there are or there have been a lot of companies in the direct-to-consumer genetic testing space. As I had mentioned, we believe a number of them have left the direct-to-consumer model behind for various reasons. It is very difficult for us to track new companies that come on the market, if they consider themselves to be under enforcement discretion, which is a practice in which FDA deliberately does not enforce its regulations because we don't require these companies to identify themselves. So we are continually having to scan the web and other tools of communication to see when new companies appear.

DR. D'AGOSTINO: So part of our deliberations and so forth is making recommendations on who should report and how the FDA should go about it? I'm just trying to clear my mind how we're going to about the question.

DR. MANSFIELD: We will ask you to discuss whether there are tests that are appropriate for consumers to order and receive the results.

DR. D'AGOSTINO: I'm talking more about the companies as opposed to the tests.

DR. MANSFIELD: Oh, the companies. We have already determined at FDA that we do not believe that enforcement discretion is an appropriate model for direct-to-consumer testing. Therefore, for any

companies that came on the market without coming to us first, we would expect to contact them and ask them to come into compliance.

DR. WATERSON: Yes, Dr. Hirschhorn.

DR. HIRSCHHORN: I would like to suggest that you correct what was probably an overlooking, that including biochemical genetic tests, which were the major tests that we had and, indeed, at the present moment, the diagnosis for one of the two disorders for which we have successful gene therapy is diagnosed using a protein-functional assay.

DR. MANSFIELD: Yes, we're aware that proteins are used to make genetic diagnoses; however, they are not widely offered at this time.

DR. HIRSCHHORN: I think if you look at gene tests, they are.

DR. MANSFIELD: As direct-to-consumer tests, I'm not sure. Our deliberations are not specific to nucleic acid testing. So in a sense, it won't make a lot of difference how we define genetic testing, but in general we have tried to limit it to nucleic acids.

DR. WATERSON: Yes.

DR. MORIDANI: This is Majid Moridani from Texas Tech.

I have a question regarding the interaction with the FDA. Did you guys also invite the large diagnostic companies, like Quest Diagnostics or LabCorp, to see what they think about direct-to-consumer marketing? Because they have all the infrastructures.

DR. MANSFIELD: We have primarily invited companies or we

have exclusively invited companies that offer direct-to-consumer testing to speak to us. Some of them have brought along laboratory partners who are performing the testing. We have not done a specific outreach to companies who are not offering direct-to-consumer testing at this time.

However, we did have an open docket after our oversight of laboratory developed tests meeting last July in which many laboratories and other companies provided us with their comments and opinions about direct-to-consumer testing.

DR. WATERSON: Dr. Tsongalis.

DR. TSONGALIS: Hi. Greg Tsongalis.

You mentioned medical claim several times in your presentation. Has the FDA expanded the definition of medical claim? Because we're kind of getting into areas that are outside of the traditional box that we usually think of.

DR. MANSFIELD: Medical claim is not defined by FDA. Medical device is. In vitro diagnostic device is. When we say medical claims, we mean those claims that arise from those devices that are considered to be medical devices.

DR. NETTO: George Netto.

The list that's listed under Appendix 2, does that apply to currently offered DTC testing, or are you talking just historically, all encompassing? Because you mentioned how some pulled out of the market

and some came back.

DR. MANSFIELD: Right. I would have to ask my colleague, Zivana Tezak, to answer that question.

DR. TEZAK: Can you repeat the question?

DR. NETTO: So Appendix 2 provides long, exhaustive tests, genetic tests, that are offered as DTC. Is this the current status? Is this the list now offered, or is this going back?

DR. TEZAK: So it is not an all-inclusive list. It's the list of tests that we took from several of the companies that are most well known. So it's tests that they're offering right now.

DR. NETTO: Right now. Okay, thank you.

DR. WATERSON: Thank you. Any other questions?

(No response.)

DR. WATERSON: Thank you very much, Dr. Mansfield.

DR. MANSFIELD: Thank you.

DR. WATERSON: I'd like to thank her for her presentation.

We will now hear from the other guest speakers. Each will have approximately 30 minutes to present and answer questions from the Panel. The first speaker is Dr. -- I apologize if I mispronounce names -- Dr. Manolio. Dr. Manolio, you may now approach the podium. Please state your name and your affiliation for the record.

DR. MANOLIO: Thank you very much. I'm Teri Manolio from

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the National Human Genome Research Institute. I appreciate the invitation to speak about genome-wide association studies and clinical applications.

One could ask what genome-wide studies have to do with direct-to-consumer testing. They were among the first studies to identify several easily measured variants associated with the risk of common complex diseases. Those are diseases caused by multiple genes rather than a single variant. So these are common, not Mendelian, conditions in general. This followed sort of a long, barren period of looking for genetic variants for multigenic diseases, many of which were failing to be replicated or really didn't really show much of anything in these studies.

And I recall, initially, when genome-wide studies first started coming out, that Francis Collins, who was one of the original progenitors of this technology, and many others would sort of preface their slides by saying, This actually works. I mean, it was really quite a surprise to us, initially, that we could get so many findings out of this.

The results have been more rigorously validated than some prior genetic findings, and they have been more rapidly incorporated into multi-gene or genome-wide panels. And as you previously heard, the pace of discovery really is accelerating.

In 2005, with the exception of maybe a handful of Mendelian -- sorry -- of variants associated with complex diseases, none had been identified by genome-wide studies. And then, in early 2005, this variant on

chromosome 1 associated with macular degeneration was reported. In 2006, a few more. And then things really started picking up, so that the pace has been incredibly rapid, so rapid that we haven't been able to keep up and update our slide. The fourth quarter is just about finished and probably has another 300 associations significant at  $p < 5 \times 10^{-8}$ .

But even three years ago, when we were back at this relatively pale-looking representation of the genome, there still were a number of companies that were offering these kinds of tests, which I suspect is why I'm here today.

So I was asked to describe a little bit about this technology for those who may not be familiar with it. My apologies to those who are familiar with it. But it's basically a method for interrogating all of the roughly 10 million common -- and by common, we mean those with an allele frequency of at least five percent. So if you have two choices, at least five percent of the population is carrying one of the variants at variable points in the human genome.

This variation is inherited in groups or in blocks so that you don't have to test all 10 million points, and the blocks are shorter, so you need to test more points the less closely people are related. But this has permitted studies to be done in unrelated individuals rather than in families, and basically one makes certain assumptions about the base pair links that are in common. And the cost has hovered in recent years around \$450, \$500

per person.

Just to explain what this does, say this is a stretch from DNA on chromosome 7. You notice that in most places everybody is the same, but every now and then you have a variant where some people have a C, some people have an A, another one -- sorry, my circles have moved. But there are various spots, about 1 per 300 bases, in which there is a variation.

These are often lined up in diagrams. You can see across the top the RS numbers, reference sequence numbers, of the various single nucleotide polymorphisms, that single-letter base pair spelling difference in the DNA. And then there are these triangles that are drawn that represent kind of the associations between these. And these can kind of throw people a bit. Here's more of a cartoon of that.

But actually we've been looking at these kinds of things, you know, most of our lives. If you order a set of maps from the AAA or wherever, you may get tables like this that say that it's, you know, 59 miles from Boston to Providence and 210 miles from Boston to New York and 150 from New York to Providence. And one could color code these and say that, you know, all of the distances that are less than 100, we'll color dark red, and all of the distances that are more than 400 miles, we'll color white. And one could fill those in and turn them on their side and make them into squares, and there you are. So it's really a very simple way of showing how these things are inherited together.

Shown here is a schematic of an example R gene from a given chromosome, and here are the exons, the coding regions and the SNPs in them, and then these SNPs are lined up along here.

So if one looks at a stretch of DNA from, say, six chromosomes in three people, one can see this SNP here is a GC SNP, and it has those two possibilities, while the white base pairs or letters are invariant across people. SNP 4, right next to it, is an AG SNP and you'll notice that every place that you have a G in this SNP you have an A in this SNP. So G and A and G and A. And every place you have a C you have G in the SNP, and so on.

This SNP over here, though, SNP 5, is a little different. So sometimes there's a G with an A in SNP 4, and sometimes there's a G with a G in SNP 4. So these do not travel together. SNP 2, on the other hand, is traveling together with SNP 3, as is SNP 1. It doesn't change with SNP 3. So these four SNPs can be considered a block, and any one of these SNPs, then, would be a good proxy for any of the other three.

Similarly SNP 6 and 7 also travel with SNP 5, so they make another block. You might have another SNP that sort of travels by itself. You can drop out the invariant DNA in between, and from Block 1 you just need to pick one SNP to represent all of them. You can pick the one with the prettiest colors, as I did here, or more often one picks the one that's easiest to assay on these various technologies. You can pick another one from here, and I've put them together and you develop a haplotype, then, stretches of DNA that

are common across populations. And, generally, because we're a young species, we tend to have long stretches of these that are most common, and a couple of them are most common and then others are much more rare.

So this was the theory behind the development of the haplotype map, or the HapMap, first published in 2005, but the data actually were widely available well before that; a second generation HapMap in 2007, a third generation in 2010, and now an even more dense SNP map that's coming up, and a map of other kinds of genetic variants that I won't talk about today in the 1000 Genomes Project, which has doubled the number of SNPs from 12 million to 24 million just in the past year.

The reason or the goals of the HapMap were to develop a more -- basically a way of doing gene-disease association studies using just the density of SNPs that you needed to find associations between SNPs and disease and not to miss any regions that had disease associations. This was a tool to assist in finding genes affecting health and disease, and one would use more SNPs for more complete coverage of populations of recent African ancestry, for example, due to their shorter LD.

Along with the HapMap, and probably driven partly by it, have been dramatic advances in genomic technology and reductions in cost, so that back in 2001 we thought we were driving a very hard bargain to get a single genotype for a dollar per genotype. And then, as these platforms developed, the number of SNPs increased dramatically, so that by 2005 we

were paying about a penny a genotype for up to 500,000 markers. And these costs have continued to fall. You notice I haven't bothered to update the slide in about four years, but basically this has continued, and now the cost has pretty much leveled out at around \$450, but the number of SNPs that one can get is getting up to the two and a half to five million range.

How does one analyze these studies? There's really a pretty straightforward analysis. There are variations on this. But in general, what you basically do is take a group of cases of a given disease, here a myocardial infarction, a group of people without that disease, and then count the number of alleles that they have of a given variant, recognizing that for autosomal variants, those on the chromosomes other than the 6 chromosome, we each have two, one for mom, one for dad.

And so basically 55 percent in this particular study of cases of myocardial infarction had at least one C allele. Forty-seven percent of the controls had a C. Sorry. Fifty-five percent of the alleles of all of these people were the C. Forty-seven percent were in the controls.

This gave a very strong chi-square and an odds ratio, which is just the cross-product here, of 1.38. So you were 1.4 times more likely to have a C allele if you were a case than if you were a control. And a very strong p-value.

One can also analyze these by genotype, taking into account the two alleles that each person inherits. So one can look at the CC

homozygote. Thirty-one percent of the cases were CC homozygotes versus 23 percent of the controls. Only 28 percent of the controls -- sorry. Twenty-eight percent of the controls were GG homozygotes versus only 20 percent of the cases. Again, a strong p-value and strong odds ratios.

And then one essentially does this 100,000 or 500,000 or however many times. Shown here are the scans for age-related macular degeneration, widely recognized as the first truly genome-wide study, published in 2005.

And because DNA is a linear molecule, you can basically line up these p-values starting from the very tip of chromosome 1 all the way down here at chromosome 22, the end of chromosome 22. And you see they had this association here, this second one, which turned out to be a false positive, probably a genotyping error.

These plots have been referred to as Manhattan plots because they look like the skyline of Manhattan. And sometimes you'll see people talking about their Kansas plots when they don't get anything. The whimsical nature of genomicists.

(Laughter.)

DR. MANOLIO: At any rate, this is another one of LV internal dimensions from the Framingham study; shown here, a nice spike right on chromosome 6 in the region of these several genes. And you can see that sometimes these are shown color-coded for the chromosomes, But, again

lined up from sort of 1 down to 22.

One of the nice things about these studies is you can kind of stretch this out, look at this region in much more depth, and shown here is the index SNP, the SNP that had the strongest association in that study, and then those that are most closely associated with it, color-coded in red.

So, again, like our Boston to Providence analogy, here is Boston to Providence, here's probably Boston to New York in orange, and then down to Washington in yellow.

Now, this particular region pretty much covers this area here, and this is sort of overlying a single gene so that it implicates that gene. It doesn't prove it, but it certainly implicates it as an association with the disease; as opposed to this, also from the Framingham study, where this wide region actually encompasses many genes, and then one needs to make some choices or do some further studies to try and figure out which it might be.

And one would note that, in general, the decisions as to which gene is implicated are made on somewhat of a personal level of the investigators involved. Very often these are not coding regions, so it's difficult to implicate a single protein sequence.

Unique aspects of these studies are that they permit examination of inherited genetic variability at really a previously unprecedented level of resolution. They permit what we refer to as an agnostic genome-wide evaluation. So you don't have to focus on coding

regions or on genes or any particular part. You just scan the genome without regard to function.

Once the genome is measured, it can be related to any trait in which you're interested. And the most robust associations in genome-wide studies have not been with genes that were previously suspected of an association with a disease. In fact, some associations, many of them, are in regions that aren't even known to harbor genes.

And as was written in 2007 by Hunter and Kraft at Harvard, the chief strength of the new approach also contains a chief problem. With more than 500,000 associations, the potential for false positive results is truly unprecedented.

I'm a big Gary Larson fan. This is a cartoon of Butlers of the World Annual Banquet, "God, Collings, I hate to start a Monday with a case like this." And here's a knife sort of sticking out of the back, and all of these false positives, potential false positives in the background.

So how does one deal with this? There was a lot written on false positives early on, even before the genome-wide era began, and pretty much the consensus has been that the best way to deal with these is to require very stringent p-values correcting for the number of associations one is testing, as well as requiring replication, as we heard earlier, in multiple populations. And standards for replicating genotype and phenotype associations have been published and are now widely followed.

As you heard, this technology is really exploding. No one can read this slide, including me even from here. I just keep it to keep track of these things that have been. As of Friday, 199 different traits, to our count, that have been studied using this technology. Some of them just sort of selected. A haphazard group of them here. Some are, you know, truly very serious and lists some without known cures. Some are continuous traits that are of interest but not greatly -- have great implications for individuals. Urate levels, for example, may have some clinical implications. Some have been done in drugs, which you may hear more about a little bit later. And this one I'd like to spend a little time on later, if we have time.

At the Genome Institute we've been trying to keep track of these. It's been a challenge keeping up with them, but we do publish a catalog of published genome-wide association studies. This is available on our website at [genome.gov/gwastudies](http://genome.gov/gwastudies). Also the way I find is through Google, just NHGRI GWAS catalog, and it pops right up.

And what it shows is all of the associations that have been published. It's updated daily, more close to daily, obtained through searches of the published literature. And in this we report the date that we've added a given variant to the catalog so that people can kind of keep track of where they are in relation to us. They offer the disease and trait, the sample size, both initial and replication, the region in which an association has been found, the reported genes. And these genes are sort of taken from the

publication, so however the investigator has defined that they are the genes that are implicated. And that's up for some debate. And then the SNP that has the strongest association, its risk allele frequency, its associated p-value, and its odds ratio. We also provide a downloadable dataset, which, we understand, has been used in a number of publications and further analyses.

And we also provide a searchable screen. So if you have suggestions on this, we have a query or a place where you can send it. Ways we can do even more work to bring this together. But we have been able to do some analyses then, based on these data, and I'd like to recognize Lucia Hindorff and Heather Junkins, who are responsible for keeping the catalog up to date. They are two saints, in my opinion, in the genome-wide field and really do a tremendous service for the field.

What have we found in looking at SNPs implicated in genome-wide studies and basically taking those SNPs that may not be the one that's directly tested on an array but is in close linkage? This equilibrium travels very closely with it in a R squared or a correlation of .9. Most of them are -- sorry. A very small proportion are non-synonymous, that is, changing the coding of a given protein, only about 12 percent, while about 40 percent of them intronic and 40 percent are intergenic, and a small number in other regions of the genome.

One could ask, well, gee, maybe this reflects some bias in the way the chips are made up, and if you just drew randomly from the chips,

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would you get a distribution similar to this? The answer is no.

Non-synonymous SNPs are vastly over-represented in the associations, given what they represent in a random selection. Intronic SNPs, a little bit and basically the same. Five prime region, which is the promoter region of genes, the area that sorts of turns -- we believe, turns them on and turns them off, are over-represented as well. And intergenic regions are underrepresented but still, you know, relative to how their proportion in the genome would still contain 40 percent of these associated variants.

The odds ratios in these associations tend to be very small. This is a distribution of odds ratios from the first, you know, couple of hundred of genome-wide studies, and you'll see that most of them really cluster down in this range. The median is 1.28 in this particular study of genome-wide associations. It's probably a little bit smaller, the median, now, because as the studies get bigger, they're picking up smaller and smaller odds ratios. But still, it's not very large, and there are still very, very few that are up in this range, and those probably are overestimates.

So what have we discovered to date? Over 80 percent of genome-wide association identified SNPs, and the SNPs in strong LD with them are intronic or intergenic. They don't really have anything, that we can tell, to do with protein coding.

Very few genome-wide studies have been narrowed to the true functional and presumed causal variants. There is clearly some selection bias

in the SNPs that are represented on the arrays. There's an excess of missense of common and of European-derived variants, which is a challenge when one starts to apply these to non-European or primarily to African ancestry populations.

Most of the associated odds ratios are well less than one and a half. Some of the traits have dozens or even hundreds of associated loci. And what has gotten a fair amount of press recently is that these SNPs explain very little of the heritability or the familial clustering in these conditions.

Just a word -- I'm challenged to see my timer there -- sorry -- a word about familiar resemblance. You may recognize these three gentlemen. One basically assesses heritability by the degree of resemblance between siblings, say, parents and offspring, for hair color, for height, for tendency to diabetes, for tendency to wear tweed, in this example.

(Laughter.)

DR. MANOLIO: But at any rate, a tendency to go into politics.

So in looking at genome-wide studies to date, those that have explained the most heritability -- and probably it should be Type I diabetes on this slide. They actually are probably explaining close to 70 or 80 percent. But given AMD with five loci, only about 50 percent of the heritability is explained here. Crohn's disease, with a far larger number of variants, only about a quarter of the heritability explained. Lupus, fewer variants,

explaining about 15 percent. Type II diabetes, many more variants, only about 10 percent. Height, probably the most heritable trait that one can measure in human populations, only 10 percent of that explained, despite 180 variants identified. Lipid levels, only 10 to 12 percent.

So this has led to this somewhat fanciful Case of the Missing Heritability, as reported by Brendan Maher in *Nature* in 2008. When scientists opened up the human genome, they expected to find genetic components, but they were nowhere to be seen.

So this, again, has led to a lot of discussion as to where is all of this missing heritability? And it's probably more than one can go into at present, but one does recognize that a given proportion of it is most likely not in common variants.

So we were looking initially in genome-wide studies, those with a five-percent minor allele frequency or greater. Probably there are some in the lower ranges, probably in rare variants that carry higher odds ratios. And all of those are investigations that are ongoing.

I think it's important, when considering clinical implications, how well these variants may predict a given disease. Shown here again, one of the strongest associations or diseases that we have explaining heritability. Just looking at ROC curves, there we see, for operator characteristic curves for predictability.

Just taking sort of a hypothetical example. If one has a variant

or a test that carries an odds ratio of 1.5, you notice that this line, which is for a test that doesn't predict anything, is right on the diagonal. That doesn't really give you very much more area under this curve. For an odds ratio of 10, which very few of these variants carry, you get a much higher area under the curve and you note that, say, at this point, where you're detecting 80 percent of your cases correctly, you're also having about a 25-percent false positive rate.

And for this variant, where you might have a fifty-fold odds ratio, which none of them have reached that far and very few other risk factors carry, if you get to 80 percent of the cases, you'll be down at about seven or eight percent false positive rate. So that would be terrific, but we're certainly not there.

And in looking at predicting AMD, now with a three-gene model, this solid line here and then various combinations of the genes individually versus no prediction at all in this diagonal line. The area under the curve with three variants is .79. But to correctly classify 74 percent of the cases, so a sensitivity of 74 percent would miss 31 percent of the controls. And to get to 80 percent sensitivity, you'd misclassify 40 percent of the controls.

So what are the limitations of genetic markers in risk assessment for disease? Most of the markers are not deterministic. Many people who don't have the markers will develop the disease. Many people

who have the markers will not develop it. Most of the genetic risk remains unexplained, and there's little or no evidence to date that interventions based on genotype will improve outcome. Genetic markers may provide additional risk information for more aggressive risk management in carriers, But, again, there's little evidence of that to date. And, yet, might there be some situations in which additional information could be useful?

I'll take a moment for a personal reflection on a very dreaded clinical condition. The clinicians in the room know that Stevens-Johnson syndrome is a horrible, horrible skin reaction, allergic reaction, often in reaction to drugs, often completely unpredictable. So a little difficult to look at, so we'll gray it out.

I saw a case of this, very much like this woman, when I was an intern, in response to spironolactone, a commonly used diuretic, and over the course of two to three days, our patient basically sloughed her entire skin surface. She then went on to slough her entire lining of her GI tract and her respiratory tract, and she died a horrible death.

It was probably the worst thing I've ever seen in clinical medicine. It made me doubt the existence of God, and yet there's probably nothing I wouldn't do to keep from seeing another case.

Happily, there have been some genome-wide studies of Stevens-Johnson syndrome that are coming out. They have not identified variants, to date, with a genome-wide significance because, fortunately, the

cases are rare and they've been too small. But there have been some other lines of evidence implicating other variants, particularly a very strong biologically plausible candidate in the HLA region for Stevens-Johnson in response to carbamazepine.

Now, if I had a patient in whom I was about to initiate carbamazepine therapy and I had information available that they carried this variant, would I use that to modify my therapy? You bet. Would I order this test myself? I'm not so sure. I might if this were a high-risk group, if the tests were readily available, if it were, you know, not terribly expensive, but I'm not so sure I would order it myself.

But if a patient came to me and said, you know, my affluent offspring gave me this genome-wide scan thing for my birthday. Do you think there's anything useful in it for me? I probably would want to scan it to determine if this variant is there in somebody that I wanted to start carbamazepine.

So clinical implications of genome-wide association testing are early on the horizon. We expect that there will be far more of them. It's sort of a challenging car to drive, if you will. You want to keep your hands on the steering wheel and your foot near the brake, but every now and then you want to put it in gear, I think, because there are certain perplexing situations in which you really want to have as much information and as many windows as you possibly can.

So I'll stop there. Thank you very much.

DR. WATERSON: Thank you, Dr. Manolio.

Does anybody on the Panel have any questions for her? Yes.

DR. LEE: Thanks for that wonderful overview. One thought that comes to mind is we also know that in the human genome there's a lot of structural variation, gains, losses, inversions. And my question is, in your experience, could these structural variants, if they overlap the SNPs that you're looking at, cause or increase the chances of genotyping errors?

DR. MANOLIO: They certainly could, and you've done most of the work in defining structural variation, so I would yield to your superior knowledge of it. But, certainly, in terms of the genotyping assays, they do yield difficult areas to genotype. Although, for the most part, the SNPs that are on the arrays, you know, have tried to -- basically try to avoid those regions because of this. And that has led to another problem, in that, how can we really then assess the role of structural variation and association with a disease? We're probably under-representing it, but you're absolutely right, it can.

DR. WATERSON: Yes.

DR. RANSOHOFF: David Ransohoff.

Can you say anything more about what you think might be promising tests or promising diseases, without naming manufacturers or something?

But what struck most was, after all the description of the biology and the technology, when you got to the area under the curve, which showed that you need odds ratios of 10 or above, and then on an earlier slide you said, And a lot of these are probably erroneous, I mean, not all of them will be. It looks like, in general, the field is producing true associations, very small odds ratios, and may therefore not be clinically very meaningful.

And I'm wondering if you, in cataloging things, have a sense of how many diseases or tests -- and also separately, are companies making claims about SNPs with odds ratios of 1.2? Is that kind of thing being put in front of consumers and doctors?

DR. MANOLIO: Yeah, maybe to take the second question. Yeah, I'm not that familiar with the kinds of claims that the companies are making. I do believe that there are -- when one gets these panels back, there are caveats. This may increase your risk a little bit. But what that means to an individual patient, how a person interprets that, you know, it's a little difficult to say.

DR. RANSOHOFF: But that is happening, that SNPs with very low odds ratios are being --

DR. MANOLIO: I believe so.

DR. RANSOHOFF: -- analyzed and -- okay.

DR. MANOLIO: Yeah, I believe so, but, you know, I'm not an authority on what companies are reporting.

In terms of the question on what do you with all of these low-risk variants, I think it's important to keep in mind -- and there are far better experts than I on the area of prediction on your Panel. But we're talking about different things in terms of predicting a disease versus using it for a therapy or for identifying treatments. And we recognize that a lot of these SNPs are likely to point us in the direction of biologic pathways of, you know, etiology of disease and that, which may well lead to important treatments.

When it comes to predicting, though, prediction is really hard, especially the futures, you know, the bear would say. And so, you know, one needs to be very cautious, and in general, these are not definitive predictive tests. You can do far better predicting diabetes measuring somebody's obesity and asking their family history.

DR. WATERSON: Any other questions? Dr. Baughman.

DR. BAUGHMAN: Jo Baughman.

Teri, could you just restate your opinion about the importance of the selection of the cases and the selection of the controls to outside interpretation or translation of the importance of the odds ratio that you do get?

DR. MANOLIO: That's a very important question, Joann, and unfortunately very often not well defined. It's getting better. But in some of the early genome-wide studies, the cases would be defined as Belgian and that was it. You know, Belgian cases of Crohn's disease. And so one really

needs to drill down, I think, into how those cases have been defined and how generalizable they are.

One of the nice things is that the widely generalizable variants do seem to cross many phenotype definitions, which is a good thing. Probably, you know, we're able to pick up these associations even with some noise in the phenotype that we're defining because the genotyping technology is so good and it's so reliable. But that's an important consideration as well.

DR. WATERSON: Any other questions?

(No response.)

DR. WATERSON: Thank you very much, Dr. Manolio.

DR. MANOLIO: Thank you.

DR. WATERSON: Our next speaker this morning is  
Dr. Stuart Hogarth.

DR. HOGARTH: Okay, good morning. I'm Stuart Hogarth, and I'm a researcher at King's College London, and I'd like to thank the FDA for the invitation to come and speak to you today. You may have noticed, I've got 45 minutes instead of 30 minutes. That's because I'm giving a global overview of regulatory trends, and the globe is a big place.

Okay. So what's the problem? And so in my view, direct-to-consumer genetic testing has become one of the foci, not the only foci, but one of the foci for the broader debate about the regulation of genetic testing,

and we know that in the United States, that policy discussion has been going on a long time. We can take it back to the Institute of Medicine report in the '90s, the task force, the SACGHS report, and then the most recent SACGHS report on oversight. And I can tell you that globally that policy discussion, you will find that mirrored in many European countries and elsewhere, for instance, Australia, Canada.

So in terms of the policy options, we have to think about what the existing regulatory landscape that direct-to-consumer genetic testing fits into, and we might identify three discrete areas of regulations. The first one is what we're really focused on today, which is the regulation of medical devices. A second one is laboratory accreditation. And, finally, the other governance mechanism that might be relevant are codes of practice, clinical guidelines, kind of soft-law regulation.

And, obviously, we've been having this very longstanding debate about oversight of genetic testing because there do appear to be some loopholes in our regulatory framework. So we have failures in our medical device regulations, and not just from the U.S. but in different jurisdictions and particularly around the regulation of laboratory developed tests. And we've got failures in our clinical lab regulations.

I can tell you that many countries, unlike the United States, do not have a comprehensive statutory framework for regulation of clinical laboratories, in terms of laboratory quality assurance. And there may be

other issues that direct-to-consumer genetic testing raises, which aren't really covered by either of these regulatory domains, issues to do with the need for pre- and post-test counseling, issues to do with storage of data and so forth that may not be entirely covered by these domains.

So in terms of our options, the first option is we can do nothing and hope direct-to-consumer genetic testing will go away. We could ban it, we can make it completely illegal. Alternatively, between those kind of two extremes, we can just try and set some rules, which I think really is what today is all about. But I'd also say we have to think about enforcement of rules because one of the things that you'll see in my presentation today is that we do have some interesting different regulatory frameworks across the globe, but it's not entirely clear whether enforcement activity is taking place.

So the way I'm going to divide up the rest of the presentation is in terms of a variety of regulatory options. The first one is looking at international treaties and standards that are relevant. The second thing we can look at is national legislation on genetic testing. Then we're going to look at the reform of IVD device regulations. And, finally, we're going to look at codes of practice. Now, in my list, I also put down enforcement of consumer protection laws, but I decided that even with 45 minutes I didn't have time to go into that.

So if we start by thinking about international treaties and standards, the two relevant kind of standards here are the Organization for

Economic Cooperation and Development, the OECD, published guidelines, Best Practice Guidelines for Quality Assurance in Molecular Genetic Testing in 2007. And I believe at least one Panel member was involved in the development of those guidelines. I'm looking at Ira Lubin.

And the second set of standards is developed by the Council of Europe. It's an additional protocol to their Convention on Human Rights and Biomedicine. It's called the Additional Protocol on Genetic Testing for Health Purposes, and that was published in 2008.

So to start with the OECD, the Organization for Economic Cooperation and Development has 30 member states that collects and analyzes data on a whole range of issues. It provides a forum for the exchange of ideas, policy development, including the development of kind of soft-law international guidelines.

It's been quite active in the areas of health, biotechnology, biomedical innovation, and way back in 2003 it did a survey on genetic testing. They looked at -- well, they were inspired by the fact that, clearly, this very kind of international trade in the rare disease area because of the kind of availability of testing often being quite restricted, and they were concerned about lack of uniformity in laboratory quality assurance.

So after that survey came an agreement that they would develop quality assurance guidelines. That was initiated in 2003 and completed in 2007. And the guidelines basically say that molecular genetic

testing should be delivered within a healthcare framework, that it should be practiced under a quality assurance framework, and it should comply with applicable legal, ethical, and professional standards. So that's a recognition that those standards may vary across OECD member states.

So germane to the discussion today are some of the kind of parts of the guidelines that address the issue of informing the patient. So the guidelines talk about the need for counseling. It should be available. It should be proportionate and appropriate. Tests results should be reported to a referring healthcare professional. Advertising, promotional, and technical claims should accurately describe the characteristics and limitations of the test offered.

I can tell you, when you first discussed that particular aspect to the guidelines, there were quite a lot of people in the room who felt that we shouldn't even be putting something in that suggested that it was appropriate that you should be advertising a genetic test direct to consumer.

And then, finally, laboratories should make available to service users the current evidence concerning the clinical validity and utility of tests that they offer. And I think that paragraph is probably very much inspired by Secretary's Advisory Committee on Genetic Testing and its notion that test providers should tell us what you know and tell us what you don't know about the tests that you're providing.

Okay. So in terms of implementation of the guidelines by

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member states, OECD carried out an informal survey in 2008. Thirteen member states responded, and most of the responding countries indicated that they had either implemented the guidelines or were preparing to do so. And OECD will now be carrying out a survey to assess what is happening, evaluate the utility of the guidelines, and to review whether any changes are needed.

And I can tell you that one of the things that there was some discussion of, that last OECD meeting I attended, was whether the whole area of whole genome sequencing was opening up new issues relevant to the guidelines.

So the Council of Europe established in 1949. It's an intergovernmental organization fostering cooperation amongst its 47 members, to protect democracy and human rights, and it's been active in bioethics since the 1980s. That work led to the Convention on Human Rights and Biomedicine. And then that was followed, as I stated earlier, by the additional protocol concerning genetic testing for health purposes, and that was adopted by the Committee of Ministers in 2008 and is in fact the first internationally legally binding instrument concerning health-related genetic testing.

So what does the protocol say? Well, it says clinical utility should be an essential criteria for a test to be offered. It says that parties, i.e., the governments who sign up, should take the necessary measures to

ensure that genetic services are of appropriate quality, and in particular, they should see to it that genetic tests meet generally accepted criteria of scientific validity, clinical validity, that there's quality assurance programs for the labs, and that the people providing services are appropriately qualified.

And then, in terms of direct to consumer, it's relevant here that the protocol states that genetic tests for health purposes may be only performed under individualized medical supervision. However, the protocol also allows for exceptions that rule. So subject to an appropriate other regulatory framework being in place, then exceptions can be made with regard to genetic tests in some cases. However, if the tests have important applications for the health of the persons concerned or the members of their family, or have implications concerning procreation choices, then an exception is not appropriate.

This kind of exception/no exception thing, I think, represents some disagreement amongst Council of Europe member states about whether there should simply be a blanket ban. And I understand the United Kingdom was one of the countries most strongly pushing that there not be a blanket ban.

So information, genetic counseling, and consent is in Article 8 of the protocols. It says that predictive genetic tests should be delivered with appropriate genetic counseling. And predictive in this definition covers both prediction of monogenic diseases and susceptibility testing and carrier

testing.

So what's the current status of the additional protocol? Well, entry into force of the protocol requires ratification by five states, including four member states, and so far only five member states have signed the protocol and only one of those has ratified it. Some key members, I should also point out, have not signed or ratified the main Convention on Human Rights and Biomedicine. So we're some way from implementation.

Nevertheless, Council of Europe staff would suggest that, in fact, a number of European countries have in effect implemented the additional protocol by the legislation that they have in place regarding genetic testing, and it's to those national legislations that I'm now going to move.

So this is mostly going to be about European countries, although I'm going to also briefly talk about South Korea. So I'm going to try and go through these countries quite quickly.

Austria. Gene Technology Act of '95 regulates all kinds of things, GMOs, gene therapy as well as genetic testing; identifies predictive genetic testing as requiring special regulatory controls around laboratories and need for pre- and post-test counseling, and the need for written informed consent. And Part IV, Section 65, states that genetic testing may only be carried out where it is at the request of a doctor specializing in medical genetics.

Okay, Belgium. Royal Decree 1987 basically restricted the delivery of genetic services in Belgium to a small number of centers; set various standards, including need for pre- and post-test counseling, and the tests should be offered on a nonprofit basis; and all genetic centers must produce annual reports detailing their activities.

Okay, France. Never entirely easy to understand the complex French regulatory system. But anyway, Decree Number 2000-570, an addition to the public health code, sets standards for laboratories, restrictions on laboratories which can perform testing, and also made statements about the need for informed consent and medical supervision in genetic testing.

And then we've also got the French Bioethics Law of 2004, which gave regulatory powers to the newly established Agence de le Biomedicine. Apologies for my poor French pronunciation. And the Agence has a wide variety of powers in relation to genetic testing, but particularly around preimplantation genetic diagnosis. There is currently a parliamentary debate about renewal of the 2004 bioethics law, and I can tell you that direct-to-consumer testing is very much on the policy agenda as part of that debate.

Okay, Germany. This is probably the most recent piece of legislation, the Genetic Diagnosis Act. So it prohibits genetic discrimination, requires laboratory accreditation, informed consent and genetic counseling. It states that diagnostic genetic examinations may only be conducted by

medical doctors, and predictive genetic examinations may only be conducted by medical doctors with specialist genetics training. And the Act establishes a new regulatory body, the Genetic Diagnostic Commission, which is going to develop guidelines and review new developments in science and technology. So essentially the Act sets the main kind of overarching controls in place. The commission is going to kind of update things and respond to developments and so forth.

Okay, Norway 1994 and Law Number 56 sets out general guidelines for research in embryos, gene therapy guidelines, and genetic testing controls. Institutions undertaking genetic testing must report regularly to the government. There's no restrictions on diagnostic genetic testing. Presymptomatic, predictive, and carrier testing does carry restrictions: cannot be carried out in minors, must be accompanied by pre- and post-test counseling, and there are confidentiality restrictions.

Okay, Portugal. The 2005 law, Law Number 12/2005, restricts the use of genetic data; so, for instance, in terms of employment, insurance. It forbids genetic discrimination. It singles out carrier, presymptomatic and susceptibility testing, and it states that they must be preceded by genetic counseling and written informed consent and they must be requested by a medical geneticist. However, these restrictions do not apply to diagnostic genetic tests or pharmacogenetic tests. The law also states that counseling should be proportionate to the severity of the disease, the usual age of onset

of the disease, and existing treatment options.

So this law is enforced, but a number of regulatory aspects of the law, in terms of how it's actually going to be implemented, needed to be developed in a final decree. That was apparently prepared two years ago, but it still hasn't been passed.

Okay, Sweden, a 1991 law on gene technologies within the context of general medical examinations. I guess they mean genetic tests. Okay. So this focuses on genetic screening. Organizations wishing to carry out testing must have authorization from the national government, and they published additional guidelines on preimplantation genetic diagnosis in 1995, which restricted the types of conditions for which you could do a PGD.

And then Switzerland. Federal Act on Human Genetic Testing 2004 covered informed consent, privacy, et cetera. Organizations wishing to carry out testing must have federal authorization, and genetic tests may only be prescribed by medical doctors (or under their supervision). Presymptomatic and prenatal genetic tests and tests for the purpose of family planning may only be prescribed by doctors who have received appropriate postgraduate training and must be provided with pre- and post-test nondirective counseling.

Okay, moving out of Europe, let's talk about South Korea. I have to say, this data is a little bit sketchy. It comes from a presentation from a conference I attended in Japan a couple years ago, and I e-mailed the

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presenter to ask him for an update, but I haven't managed to get an update. So this is what I know from the meeting I attended.

There was an advisory committee convened by the Korean Society of Medical Genetics that reviewed common direct-to-consumer tests. They were funded from the Ministry of Health and Welfare to do that. And then, since 2007, 14 genetic tests have been banned and six have been restricted in terms of availability. So banned tests include tests for obesity, diabetes, alcoholism, and the tests that are restricted in how they can be accessed include tests for BRCA and APOE for Alzheimer's. Direct-to-consumer genetic testing is prohibited in Korea now.

And they've also established in 2005 a new body, the Korea Institute of Genetic Testing Evaluation. That's been established with support of the government. It's going to have responsibility for quality assurance and evaluation of clinical validity of tests. I'm really not certain about how far along they are in developing this new regulatory framework, but that was the direction in which they were going.

Okay. So what can we draw in terms of generalizations from this kind of overview of national legislation? What we can see are restrictions on who can perform testing, on who can order testing, and how the data can be used. We can see standards for how genetic testing is performed, in terms of quality assurance, in terms of protection of privacy, informed consent, and so forth. And we can see clearly that these countries which have passed

these laws believe that genetic information is special, but that some genetic information is more special. In particular, frequently predictive testing and prenatal testing seem to be singled out for more strict regulatory treatment.

But I think these pieces of national legislation also raise some questions. The first question they raise is what is potentially -- I don't think it actually is, but is potentially a global market.

- Are direct-to-consumer genetic testing companies complying with national legislation?
- Does such national legislation affect cross-border trade?
- Is there any evidence of enforcement activity in these different countries that have this legislation?

I'll be honest. I don't know of any enforcement activity in most of these countries, apart from South Korea.

- Are clinical standards applicable to rare disease testing appropriate for susceptibility of pharmacogenetic testing?
- Is counseling necessary for all types of genetic testing, and if so, how much is proportionate and appropriate?
- Does the specialist expertise of healthcare professionals trained in clinical genetics give them particular competence to deal with susceptibility testing?

Because genetic counselors aren't actually trained, I think, to

deal with susceptibility testing. That's not the focus of their training. Their focus is rare diseases.

- And does requiring a doctor's involvement in the provision of genetic testing stop bad tests getting onto the market?

And I would say the answer to that question is no. Okay. So if we do want to stop bad tests getting onto the market, then perhaps we need to look to our IVD regulations, and I'm going to talk briefly about the situation in Australia and the situation in the European Union.

So the European Union. We have a harmonized approach to the regulation of in vitro diagnostics. We have a directive, the in vitro diagnostics directive, that's implemented in each member state. But it has a number of significant limitations in terms of being an instrument that could actually have any purchase on the issues that we're discussing today.

So the first limitation is that most tests, including genetic tests, are classed as low risk, so there's no independent pre-market review of them. So you can basically put on the market whatever the heck you like.

The second question is around laboratory developed tests. Now, I'd say that's something the UK and something, I think, the staff of the European Commission believe that commercial laboratory developed tests, under the terms of the directive, are medical devices. But interpretation and enforcement varies across member states. And I think the implications of

regulating LDTs as medical devices was not thought through when the directive was developed.

So, for instance, what's the equivalent of a product label for a laboratory developed test? That's quite important if you think that truth in labeling is one of the main things that you get out of the regulation of medical devices.

And they certainly hadn't thought through the implications of direct-to-consumer testing, because if you produce a direct-to-consumer kit, the kind of cholesterol kit you can buy in Walgreens or wherever, then under the European regulations, we would have a separate regulatory pathway for that. But it's not at all clear that that regulatory pathway applies to direct-to-consumer genetic tests which are LDTs, not kits.

Okay. And the current legal consensus from guidance that we've gained from a number of member states and the commission is that laboratory developed tests performed outside the European Union are not covered by the directive.

Now, personally, I think they're wrong in their interpretation. I think it's one of these issues that nobody thought about when the directive was written. I don't think the directive either rules it in or rules it out, but that's where we are at the moment.

And then, in terms of the scope of review, when we do review tests, there seems to be some real doubt about whether the directive is really

just focused on analytic validity or it's also focused on clinical validity of tests. And clearly a lot of the concern in the domain that we're talking about today is around the clinical validity, the clinical claims of the tests, that are being made for the tests.

Okay. So I did an interview with a U.S. molecular diagnostics company in 2006. I said, What do you think of the European regulations? They said, We like them; there aren't any. And they laughed.

As a matter of fact, Jeff Shuren, the head of CDRH, recently got into a bit of trouble because he told Congress that the European medical device regulations weren't very good. I think Jeff's right.

Okay. But fortunately the European Commission is quite keen in trying to strengthen our regulatory system. So they've had a consultation on all the medical device directives and then on the IVD directive in particular; 2008-2009 we had these consultations.

So the issues that they've raised. They suggested that we adopt a new risk classification system, the Global Harmonization Task Force model, which would essentially mean that genetic tests would be made moderate to high risk and would be subject to pre-market review. They suggest that we review the essential requirements and flagged up issues of clinical validity and clinical utility of tests. They suggest that we need to clarify the status of laboratory developed tests and that we might need special measures for direct-to-consumer genetic testing.

So the consultation closed late last year. Oh no, actually September last year. And the commission is currently reviewing the feedback it gained, and we expect to hear something from the commission, in terms of what they're proposing as the way forward, sometime later, I think, spring this year.

Okay, Australia. So Australia has a completely new set of regulations for in vitro diagnostics, and as part of that new regulatory framework, they've put restrictions on IVDs for self-testing, and they basically said that certain types of self-testing will be prohibited; so IVDs used to test for pathogens or diagnose notifiable infectious diseases, tests used to determine genetic traits, and tests for other serious disorders, for example, cancer or myocardial infarction.

And Australia has also addressed the issue of regulation of laboratory developed tests, medical devices. It said that LDTs are medical devices and has come up with a very interesting way of addressing the regulation of LDTs. I can tell you that there was a quite a lot of clinical resistance to LDTs being classed as medical devices in Australia, and this is the compromise they've come up with.

So high-risk tests will be reviewed by the Therapeutic Goods Administration, but then low- and moderate-risk tests, for them, laboratories have to register with TGA and they must notify them when they introduce new tests. But the actual validation of tests is carried out by bodies

responsible for laboratory accreditation, so NATA and NPAAC. However, TGA participates in the standard setting and can intervene where there's a concern. So, in effect, with these low and moderate-risk tests, TGA has given themselves a kind of oversight view, but they allocate most of the regulatory work to third parties.

Okay. So the final kind of regulatory option that we're going to explore, codes of practice guidelines, soft law, we're going to look at Japan very briefly and then the UK.

So Japan. In 2005, the Ministry of Economy, Trade and Industry published guidelines on protection of individual genetic information. And then, following that, some of the companies in this space were inspired to set up their own kind of trade body, the Consortium for the Protection of Individual Genetic Information, which encouraged compliance with these guidelines. And then they took it further. They looked at the OECD guidelines on quality assurance, and they basically said, We should follow these guidelines as well.

So they've got a kind of industry self-regulation framework developing within Japan. Nevertheless, there is concern about the DTC genetic tests that are available, and the Japanese Society of Human Genetics published comments on this issue in 2008.

Okay. So the UK. The interesting thing about the UK is we were kind of pioneers in the regulation of consumer genetics. Way back in

'97, when a UK company decided that they wanted to offer carrier testing for cystic fibrosis direct to consumer, people got very upset about it, and we came up with what was kind of classic British regulatory compromise. Rather than kind of passing some legislation, we said, well, we're going to have a voluntary code of practice. But the code of practice had on the front of it, If companies don't comply with this, then we will pass legislation or we may pass legislation. So it was the threat of legislation hanging over them.

So it was the Advisory Committee on Genetic Testing which developed this code of practice and guidance, setting out a whole series of standards around laboratory accreditation, confidentiality of data, need for counseling, need for information about the test, its scope and limitations, its accuracy, significance and how it should be used, the kind of information the test provider needs to be given. And so that was way back in 1997.

The company that was providing the testing decided that it wasn't economically viable to provide counseling as well, so they just stopped doing it, and after that we really didn't have any kind of direct-to-consumer genetic testing companies for a while.

We had a review of all the advisory committees for biotechnology in the UK, and a reorganization. We wound up the Advisory Committee on Genetic Testing and created the Human Genetics Commission, which was purely supposed to give advice to the government, very much like SACGHS was doing until recently in the United States. Oh, sorry, I've gotten

ahead of myself.

Okay. So the code of practice also outlined where direct-to-consumer testing was acceptable. It was basically just carrier testing, and they thought that everything else, including susceptibility testing, it was unacceptable to offer direct to consumer.

Okay. So basically we wound up the advisory committee. We created the Human Genetics Commission. The Human Genetics Commission was supposed to be an advisory body. It wasn't supposed to do anything regulatory. So at that point we had no one in charge of the code of practice. The code of practice that was listed, we didn't have a body in charge of it.

Sciona came along and said, We want to offer our nutrigenetic testing. And the only relevant body who could review it against the code of practice was the Human Genetics Commission. So the Human Genetics Commission said, We're not actually regulators, but we'll do this because there's no one else to do it. But they also said, well, look, we need to sort this out. We need some clarity about what the regulatory framework is.

So they launched what was the, as far as I know, still the largest kind of public deliberation on -- a policy deliberation and public consultation on direct-to-consumer genetic testing ever carried out. So we had all kinds of different -- we had surveys, we had focus groups, lots of different forums, consultation with the public, a draft report that was open to public consultation, and so forth. And they came up with a whole series of

recommendations. So they didn't say there was a single solution. There were a whole series of things that all needed to be addressed to create a comprehensive regulatory framework.

So we needed pre-market review of tests, medical devices. They didn't want a statutory ban of direct-to-consumer testing, but they thought that some tests should not be offered direct to consumer, especially predictive testing. They thought there should be a code of practice; that we should discourage direct-to-consumer advertising; that where adverts were allowed, there should be stricter controls on them; that we needed to educate the public and that we needed an independent body providing information about genetic testing for the public.

Okay. Basically, that report came out in 2003, and the government did nothing. It sat on the shelf like so many worthy reports do. And then, by 2006-2007, the market was picking up a bit, so the Human Genetics Commission decided to write another report, and it basically reasserted its key recommendations from the Genes Direct report.

At that point it was clear that progress was going to be slow on most of the policy recommendations, but it was possible that the Human Genetics Commission could actually help to convene some work around the code of practice.

So we had an international meeting to discuss the code of practice in 2008. Industry were heavily represented. We had DNA Direct,

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deCODE, Navigenics, 23andMe, Genetic Health, and our British trade association, BIVDA. And there was overwhelming support for a code of practice. Companies saw the value of a quality mark. There was agreement that we should have risk stratification to determine the regulatory approach, but that there should be minimum standards which apply to all test issues, such as a consent, confidentiality, laboratory quality assurance, et cetera. So that was 2008.

So we formed a working group in 2009. That working group included Navigenics and deCODE. And we decided to develop, not a code of practice, but guiding principles for a code of practice. So the recognition here was that it's an international market. We wanted an overarching document which could apply across different jurisdictions with different legal frameworks and serve as a basis for developing codes of practice specific to those jurisdictions.

The other reason for going for guiding principles rather than a code of practice, quite frankly, was that although there was a lot of support for a code of practice in the 2008 meeting, nobody wanted to step up to the plate and say, well, we'll take responsibility for that code of practice. We'll develop it and we'll enforce it.

Okay. So we had a public consultation on the draft principles. That was international. It was a very wide divergence of views on what categories of tests should be available direct to consumer. And yeah, I think

that's probably the issue on which people diverged mostly. And we published a final document in 2010. It basically said that the tests for inherited/heritable disorders required pre- and post-test counseling. Other tests may also be best delivered with medical supervision and that we need to consider a whole range of factors, from the severity of condition to its impact on clinical management, familial implications, et cetera, in deciding whether medical supervision was necessary.

So in terms of what we're going to do next in the UK, we're rather like SACGHS here in the United States. The Human Genetics Commission is, in fact, now being wound up, and there's no move in the UK to transpose these principles into a code of practice. So, in fact, it seems to me that the United Kingdom may be unique in the world in having diminished its regulatory control over direct-to-consumer testing over the last 15 years.

I should also point out that although the focus of the Human Genetics Commission's work in the last kind of year and a half was on the code of practice, the commission remained committed to the view that the code of practice was only part of the regulatory solution. Direct-to-consumer tests also need to be treated as IVD devices and subject to pre-market review.

So conclusions. Clearly, the number of countries imposing legal restrictions on direct-to-consumer genetics has increased at the same time as the number of companies offering direct-to-consumer genetic testing has been growing. It seems to me that rulemaking activity hasn't been matched

thus far by enforcement activity, but I believe that that will probably change if the direct-to-consumer testing market grows. However, I think that's quite a big if. And Liz Mansfield has already talked about the fact that, with some FDA activity in this space, companies have already been changing their business models or closing.

The sustainability of direct-to-consumer business models, I would argue, is completely unproven. We've already seen companies struggling. Sciona, one of the pioneers, closed in the last two years. deCODE went through bankruptcy proceedings. We've seen layoffs at 23andMe. I think all of this speaks to the fact that it's actually very difficult to make money selling tests, genetic tests, direct to consumer.

And we've seen companies who entered the space as DTC companies shifting their focus either entirely or partly to try and supply the tests through physicians; and I think DNA Direct, the most notable company in terms of that change, but Navigenics, although still offering tests DTC, have also been developing relationships with physicians.

So because the business models' sustainability aren't proven, I would tend to disagree with the people from 23andMe who recently wrote an article saying that the direct-to-consumer genetics testing train has already left the station, that it's a kind of unstoppable force. I would suggest that, in fact, we're still laying the rail tracks and that the regulatory framework is probably the most important part of those rail tracks, and what we're trying

to avoid is disaster. Okay, thanks.

DR. WATERSON: Thank you very much, Dr. Hogarth.

Does anybody have any questions? We'll start over there.

DR. RANSOHOFF: David Ransohoff.

Can you say more about what the word clinical utility might mean, if there's any kind of agreement on it? It got used in the Council of Europe's early statement. The words clinical utility were there. And it also got used, you noted, in the 2008 British -- the UK general principles thing.

Is there any kind of agreement on this, and in particular, does clinical utility mean something like more benefit than harm? Or does it relate to clinical outcome? Or does it relate to I feel empowered and good when I know this sort of thing? Have the various groups grappled with that issue of what utility actually means?

DR. HOGARTH: Yeah. I'm just trying to think if the Council of Europe has a clear definition. Off the top of my head, I can't say. What I would say is that it's one of these issues where I think there's been a significant amount of policy transfer, sharing of ideas, particularly facilitated by public health, the genomics movement. So people like Murin Kerry (ph.) talk to their counterparts in the UK and Europe more broadly.

So I think, you know, if we think about the ACE framework that was developed in the states and its definition of clinical utility, which I think speaks primarily to clinical outcomes, but you can extend it to cost

effectiveness, is kind of the definition people are working with. But I think, in broad terms, I think what the Council of Europe are getting at is, is this actually going to make a difference to how you manage patients? Is it actually going to have some significant improvement on patient outcomes?

DR. RANSOHOFF: Because if it's outcomes, that's a very, very, very high bar, and from the few meetings like this that I've been to, the issues of how the test, sort of what bar you have to hurdle is a really, really, really big deal. For example, demonstrating clinical utility for the U.S. Preventive Services Task Force, to parallel that sort of effort, that's a real major, serious thing, and this world seems to be, at least historically, operating under somewhat different considerations of what utility really means. And it sounds, from what you said, like it's somewhat of an open issue here.

DR. HOGARTH: Yes. I mean, clearly, the utility of biomarkers takes a very, very long time to develop. Decades, in general. And we're still arguing over PSA.

DR. NETTO: George Netto.

Thank you for your presentation. I would like to see what's your thoughts why UK restrictions seems to be much less on DTC compared to other Europeans that you shared with us? Any ideas why?

DR. HOGARTH: Well, I guess we kind of have this thing of being halfway, one foot in Europe and one foot in America. We have a tendency to want to adopt light-touch regulation where possible, which is kind of a

tradition that isn't shared by all our continental counterparts.

I think the specter of eugenics, that shadow looms much larger in parts of Europe that were subject to Nazi occupation, oh, indeed in Germany and Austria; so I think the historical factors there, as well as just general cultural kind of propensities in relation to regulatory frameworks.

What's interesting about the UK situation is we probably have the most sophisticated governance arrangements for clinical genetic testing, within the NHS, of anywhere in the world. We've got both the laboratory quality assurance covered and evaluation of tests using our new gene dossier system. But none of that applies in the commercial space.

DR. LUBIN: I have two questions. The first question is, do we have any data on how the tests are being offered and used when there are -- when the companies are beginning to partner with physician practices? So that's question number one.

And question number two is, do we have any data in terms of things that you or others have done in terms of the ease of which or the volume of cross-border activity of these kinds of tests?

DR. HOGARTH: I think the answer is just no to both questions. I think it's important to note, as well, that I suggested that partnering with physicians was a trend that was being adopted by some of the U.S. companies. But actually, if you look at companies in Europe, where there are restrictions on who can order a genetic test, that model has already been in

place much longer. For instance, in Austria, a company called GENOSENSE do nutrigenetic testing and some susceptibility testing. They've had that model of partnering physicians since they started because of the legal restrictions in Austria.

In relation to data on volume of testing, what's happening, no, we don't have that kind of data. And I think that the fact that we don't have any data at all, partly again speaks to this issue of the fact that although we have rules in place, there's not much enforcement activity because just trying to gather some information, which is what FDA is doing today, is kind of another one of the core functions of a regulatory system, and I'm not sure even that's happening.

DR. MORIDANI: This is Majid Moridani.

I also have a cross-border question. When a test is ordered and the test result is released, is that something that is valid in another country, or it has to be ordered by a licensed physician in that country and be performed and released within that country? Like UK versus France, for instance.

DR. HOGARTH: Yes. So I think that certainly, in general, the regulatory framework has had to be developed in a way that's fairly flexible, because if we think about this in terms of rare disease testing, then there are issues about, you know, the necessity of cross-border trade. It's not entirely clear to me, this question of whether the physician has to be within the

country and under different pieces of legislation. However, some of the pieces of legislation clearly are authorizing who can order the tests within their country. So presumably, within those countries, they'll have that type of legislation. Then there is the kind of control that you suggest. But, again, I think all of this is just completed untested, in a sense.

DR. WATERSON: Thank you very much. I think we're going to have move on because we have to keep on time. Sorry.

Our last speaker before the break this morning is  
Dr. Nancy Wexler.

DR. WEXLER: Thank you very much. It's really an honor and a pleasure to be here, and I appreciate the chance for being part of the discussion.

I'm going talk today about three aspects of what I call toxic information: the value or harm of this information, what should be included in protocols to deliver this information, and the setting; should we do it in direct-to-consumer tests, or what other kinds of venues do we have?

I'm going to speak personally because I think that sometimes, when your own personal experience is brought to bear, for one thing, you see my biases, but I think I share these biases with almost anybody in the world with DNA. Since everybody has DNA, we all have something that we are nervous about, watch out for, or feel we are destined to get in the future.

When I was 22, my sister Alice, over there, 25, we discovered

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that our mother had just been diagnosed with Huntington's disease. Our grandfather died of Huntington's. All of my uncles, my mother's brothers, all three died of Huntington's disease. And she was just diagnosed at the age of 53. My sister and I realized that this could be our future. And that was 1968. There were not very many possibilities around for predicting your future, and there were certainly no tests. We desperately wanted a test to say we were not going to get it, but we were not that sure we wanted a test to say this definitely was our future. If my sister and I inherited my mother's gene, then we each had a one-in-two chance of developing -- well, getting the disease and passing it on to our children.

Fortunately our father, in 1968, started the Hereditary Disease Foundation, and we started looking for cures because we thought, okay, if we could find a cure, a test would have a context. The Hereditary Disease Foundation had the wonderful good fortune to find Dr. David Housman and Jimmy Gusella in Venezuela, for us to go Venezuela and look, with a restriction fragment like polymorphisms, which just been really invented in 1979, for the Huntington's disease gene.

The pessimists said it never could happen. The optimists said it would take 100 years. We said let's get going. Steve's smiling because he knows this history. And we went down to a little stilt village where we found actually the largest family so far still described with Huntington's disease. All 18,000 people were the descendants of one woman living in the early 1800s,

appropriately named Concepcion.

So we started looking for the gene and looking for the gene, and much to our astonishment, in 1983 we found a DNA marker which said that the gene is on the top of chromosome 4. And 10 years later -- I'm going to just skip a huge amount of arduous work -- we actually found that the gene is precisely on the top of chromosome 4. It's the same gene worldwide, which means that any test that's developed for the gene should work worldwide because it's precisely the same place.

This gene has, normally, a certain span of CAG repeats. Up to around 34 CAG repeats, and you have a normal life. But between 35 and 39, you may or may not get Huntington's disease. Forty repeats in a row, you're destined, if you live a normal lifespan, to get Huntington's. And 60 repeats in a row, you'll get it less than 20. So you can see that the numbers and the test itself really have to have a tremendous amount of accuracy.

I'm going to just skip ahead for a moment to when we are actually providing this test to people, because we encourage people to get multiple samples. And one particular woman, I had four different samples taken and sent to four different labs. She had one that was 38, one 39, one 40 and one 41. So do I tell her that her life is free of the disease, that she may or she may not get it, or do I tell her that, you know, Huntington's is definitely in her future and she's destined to have it? So these things are very, very complicated.

The ages of onset, again, a huge amount of variability. What we do not appreciate is that when we started publishing about the relationship between repeat size and age of onset, that many people would read -- the family members read the articles and said, well, you know, my life is going to be over pretty soon, so I might as well either live dangerously or commit suicide.

Now, the advantage of the Huntington's gene has been fabulous for research. We've been able to put it in creatures, in cells, in animals. But I think the frustrating aspect for everyone is that the treatments and cures really are not that different than in my mother's day in 1968. We're using the same things, so we need to do better.

In 1984, when we had the marker, we actually realized that that marker could be used for diagnostic testing. And then 10 years later, when we had the gene, the gene itself could be used on anybody walking into anybody's office. And in 1994 people were really not very sophisticated about what this meant.

So a group of families and professionals, the International Huntington's Association and the World Federation of Neurology Research Group on Huntington's, got together and we developed testing guidelines. These guidelines are still in place and they're really accepted worldwide, probably because the treatment and cures has not varied since 1984, really. There's only been about 10 percent of people utilizing this test throughout

the U.S. and Europe.

A critical aspect of the guideline is that anybody that takes it should have very, very appropriate and rigorous counseling, and they should also go with somebody to hear the information because you block it out, and also for the information itself when you get your test results. You can't be coerced into taking it. Critical. You know, this was since 1984. I think we made the first guidelines anywhere, and I'm pleased to see actually many of them still retain the age of majority, you know, for other diseases that have a huge impact.

You have to decide for your own self, your personal self, that you want it at the age of 18 or older. So this means that your parent can't just get nervous about what your future is and to take your sample and send it in to a lab, and then it's the violation of the privacy of the child; we forbid it. Now it doesn't mean it doesn't happen and that people don't push you to do it all the time.

Finances shouldn't be an issue. Of course it always is. And discrimination should not be an issue, which it is in this country.

Now, one area where prenatal testing, I think, developed some significant benefit is that sperm donation and ova donation makes a difference and prenatal genetic diagnosis, or PGD, has really made a huge difference versus a technique where you can just take your -- cell off an embryo and test it for the presence of span and repeat for the Huntington's

gene. If they're just normal genes, you implant that embryo and you have a normal child.

We developed what we call non-disclosing guidelines because many people did not want to know their own status. They just said, I don't care. You know, my future, I can't change it, but just make sure I'm not passing this on to future generations. So as long as you just put in normal embryos and don't tell the person their own status, then it's actually, I think, been very effective. The problem is in vitro fertilization. It doesn't always work, it's very expensive, and it's not insured in the U.S.

Now, a survey done in 1998 looked at the numbers of people who had catastrophic reactions to this information. Forty-four individuals from over 6,000 people worldwide had a catastrophic reaction to receiving the test information. Five committed suicide, 19 attempted suicide, 20 were hospitalized. I'm positive this is actually very underestimated. Of those people who had a catastrophic reaction, 80 had expanded repeat, 20 were normal, which is sort of surprising to people. Well, why were they -- you know, what happened?

And a friend of mine actually, who had a normal test result, went into the shower and pulled a gun. He did it in the shower so that his family wouldn't have to clean up the mess. Now, can you imagine that you could go to Wal-Mart and get the HD test and it is wrong, or any other, you know, downloadable information and it is wrong, and your family members

commit suicide? You know, this happens all the time. 23andMe, you get your information downloaded.

Another friend of mine who had a genetic test said, well, I'm going to just go out and drive into a tree because then nobody will know it's a suicide. They'll just think I got sleepy because, you know, I went out.

So these are the plans that family members have, and we need to be very aware of this when we're talking about the possibility of direct-to-consumer testing.

And I really congratulate the FDA for looking at what's happening now in direct-to-consumer testing. Right now there are 31 companies offering genetic tests for about 450 diseases, genes and traits.

Now, you can see the -- and these are supposed to be, you know, very recent, so they're probably accurate: athletic performance gene, attentive/social gene, back pain gene, eye color gene, faithfulness/loyalty gene; wouldn't you want to buy that, huh? Okay. And we're older people. I'm going to buy that one for sure. Metabolic health. Ask about the -- muscle performance, musical gene. I want that one.

Now, there's some of my favorite ones up there, right at the very top, you see, there's propensities for teenage romance genes, right next to response to Viagra genes, right next to recurrent pregnancy loss, right next to risk-taking genes. So why wouldn't you want that? You know, I think we need to be aware of the seductiveness of these kinds of over-promises.

My Gene Profile, which actually had a lot of those, some of the most weird genes and traits, I think is actually very dangerous because it's like one of the most egregious examples of what's out on the web. You can take the inborn talent test for your kids, okay? Now, you're not supposed to be testing other people, but, hey, why not? Okay. So on the web, you have a little baby, you buy a buccal swab test, okay? You go off and you take that little -- your baby.

Now, you're not promising not to test for Huntington's. Well, little babies often have choreas, so little things like that, parents freak out. Oh my God, my baby has Huntington's. Let's go get the buccal swab test and make sure that the baby's, you know, going to be okay. And sometimes, you know, that baby might've been Woody Guthrie or get sick at 92.

But anyway -- 1,000, almost \$400, you can find out your baby and your children's inborn talents. Instead of having horrible, ferocious arguments with your children about what they -- you know, doing their homework or not. You know, you can get their inborn talent tests, and you get assured of high accuracy, top American technology, certified, all ethnicities, highest number of genes tested.

Now My Gene Profile. It goes on to promise something which, again, I think is very sinister and egregious and pretty typical of what I found out there on the web. Because, while you're testing for your baby, their inborn talents, why not test for your own, you know, catastrophe genes?

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What kind of things do you have lurking in your background? As a health-conscious parent, you know, it's your responsibility to know so you can help your doctor prevent future health problems, you know, what you've inherited from your parents, grandparents, and even great-grandparents.

Now, why wouldn't all of us want to go into our doctor and say, you know, Look, I'm really worried about what runs in my family. Can you check it out? But they're assuming that either we're too stupid to do that, the doctors are too stupid to ask, or we don't have any common sense.

And actually this paragraph here, from the same company, I think is -- it just makes me furious. "The Disease Susceptibility Genetic Test is available for you to take today. This is thanks to the world class genetic scientists who worked on the Human Genome Project and the countries who poured billions of dollars in genetic research. These elite scientists uncovered the secrets behind genes, DNA and gene mapping. Because of this in-depth gene mapping knowledge, we can determine your inherited health risks," which to me felt like raping the Human Genome Project, right in that paragraph. I'd say we didn't do our work so that you could rip people off with bad information.

So you see, you know, they actually are promising, and we've seen labs that are supposedly CLIA compliant, which they may be, to test for 108 actual diseases: emphysema, cancer, lung cancer, diabetic angiopathy, cardiomyopathy. You know, these are bad, nasty things, so a lot of people

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would say, well, why shouldn't I find out about these? Alzheimer's disease, epilepsy, Parkinson's. You know, what are they actually testing for? Bladder cancer, prostate cancer, breast cancer. I mean there are, you know, more and more of these actual diseases that they're promising to check for.

My Gene Profile Disease Susceptibility Genetic Test complete package, over \$18,000. But during this global project launch, you can get the complete Disease Susceptibility Genetic Test, you know, not 18, not 2, for a mere \$1,897 you can get information which purports to be for the serious, you know, health-interested, curious, probably extremely rich, white middle-class person. And this is going on all the time.

You know, if you look at Amazon, there's a genetic cancer screening test. The test kit is for \$12.99. The \$639 lab fee not included.

So even NPR recently did, I think, very good coverage of the fact that the Government Accountability agency and the FDA is playing god, saying, you know, what kind of chaos is going on out there? You know, we just cannot do this. There's been a lot of information about, you know, just sort of taking a why should we be doing this and the ethics of it.

Now, another part of my life, which I loved, actually, was serving for a long time as the chair of the ethical, legal, social issues working group, and I think the task force back in '97 looking at some of these issues, and even back then I think we recognized that we needed to learn a lot and be much more rigorous about providing those tests.

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Their recommendation in '97 is that no clinical laboratory should offer genetic tests whose clinical validity has not been established on methods collecting data under IRB-approved regulations. An agreement with the FDA. And also what tests should be used, that predicting future diseases be rated -- given a rating of high complexity. But I think, really, we have a great deal more to go.

One of the issues in the states is just the lack of being able to have a doctor. And for the genetic -- Huntington's genetic test, because, you know, as a person at risk for Huntington's, I'm actually uninsurable. I get insured because I work at Columbia University and I'm part of a group. But the category of a person at risk for Huntington's is an uninsurable category.

So when we do the HD genetic testing, we say to people, you know, as part of, again, the guidelines, Please make sure you know that you could lose your health and life insurance and disability insurance, you could lose your job. And it happens. We suggest that people pay for it out of pocket, if they can afford it, because then the insurance company can't possibly know what the outcome is. And, again, since they're doing it for multiple times, you know, that can be very expensive. Many people get it tested under an assumed name just for privacy.

So I think one of the difficulties also in the states is the fact that so few people have doctors. And so time to introduce something that's very sophisticated and that's very unique to our circumstances requires a lot of

time and energy and effort and thought. I think that the Obama Administration's healthcare reform actually is going to have a big answer to trying to bring more doctors into the fold and giving people the lack of -- you know, 2014, there will be no preexisting condition exclusions. So I think this will actually make a huge difference. The lack of caps on insurance is going to make a difference because people with genetic diseases are getting better treated, they're already living longer, thank God, but they're also, you know, ruining their lifetime caps. So for the first time, I think that people will actually have a chance to actually have a doctor and go into a doctor and have this conversation.

Our country right now has the highest infant mortality rate in the developed world. You know, I think it's worse than Cuba. So I do think that we have a huge -- we can take advantage of this information, but we have a long way to go.

My own feeling is that the direct-to-consumer tests should be -- the company should be closed and that should be eliminated. I think the direct-to-consumer tests prey on our worst aspects. They cater to snobbery in the rich. They are against doctors because we are too stupid and benighted to do the right thing by our patients. They take advantage of the Human Genome Project by raping its information and using it for their own commercial gain and avarice.

We need to insist that all testing of DNA and all biochemical

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tests that reveal any critical information must be analyzed in strictly controlled laboratories regulated by the strictest rules of the FDA, which must be strengthened. CDC, CLIA, all of the diverse patchwork of authorities should immediately, you know, hopefully guided by your input, strengthen the rules and make new ones if they need to. We need to reassess the state of the art and the science because it changes daily.

All direct-to-consumer companies should be closed. If their information is so shoddy in relation to, and mistaken, why would they be accurate for testing ancestry or paternity? Certainly all of those that offer so-called clinical information about susceptibility and traits and diseases should be immediately closed.

Funds could be spent on supporting better research and developing treatments and cures. Those of us who put our heart and soul into finding treatments and cures deserve no less.

And when we went to Venezuela back in 1979 to look for the Huntington's disease gene, we did not think -- we did hope that that information would lead to new treatments and cures. We did not think that this information that's been the birth of the Human Genome Project would be used to create invalid, unreliable, unregulatable toxic knowledge. We did not expect to be raped.

Any questions?

DR. WATERSON: Anybody have any questions for Dr. Wexler?

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Start over there. Steven.

DR. HERSCH: Thank you, Nancy. That was very powerful. I have a couple of questions along the lines about risk/benefit, but also your thoughts about some of the experience in Huntington's disease. You mentioned some of the data about suicide and hospitalizations. Those are kind of like the SAEs. They're the really catastrophic stuff --

DR. WEXLER: Right.

DR. HERSCH: -- that you can have information about. I was wondering if you could talk to us a little bit about sort of the daily burdens of living with a known, or maybe even not factually known, but potential risks.

DR. WEXLER: I think that's, you know, very much an underestimate. And even people that I know who've been hospitalized or committed suicide are not part of those numbers.

I think it's very hard for people to think that they made a mistake. Some people that I know, they got tested and said, If I could do it over again, I wouldn't do it. But that idea, I'm afraid to think about it because I'm afraid it's going to take up housekeeping in my mind. Very often people say that if they'd had better counseling to deal with the problems of being at risk, or their family or affected parents, that they would not obtain the test.

And then, once they do take the test, I think it's -- they have to really keep it quiet because it can affect their job, their insurance. There's, I think, a lot of issues around, if you know somebody has an expanded

repeater, you know they're at risk. They get watched all the time. So they're in a very precarious situation. Even being public about being a Huntington's family can affect their job performance, whether they're hired, whether they get tenure. So I think that there is just a tremendous amount of extra baggage.

And very few people that I've met who actually got the test, some of them used it to have children that didn't have Huntington's, but they used PGD. But still, you know, with non-disclosing, they didn't have to do that. And had they known that that was an option, you know, they would've done something differently.

So if we had a fantastic treatment that made a difference, that you could start early, then I think that might be different. But even then, some of the treatments that we're doing, you know, experimentally like, you know, creatine CoQ that you're working on, many people say, well, give it to me, but I just don't want to know my genetic status. I'd rather take, you know, maybe a benign drug.

If you were going to use RNA or oligos or something where you really needed to know somebody's gene status, that'll be different. But then you'd have more potential for actually having a valuable therapy.

DR. TSONGALIS: So thank you for sharing your experience. As a clinical lab director, I think I can safely say that the majority of healthcare providers in the U.S. couldn't interpret a genetic test result if their life

depended on it.

And so do you think there's any possibility or any way that we could take good and bad experiences that we've already realized from direct-to-consumer testing and probably other experiences that we're going to have and turn that around into an educational possibility for healthcare providers?

DR. WEXLER: Yes, I think that's a good suggestion. Right now, for example, there's nothing forbidding any of these companies to offer Huntington's tests. It's not illegal. And DNA is DNA. They're giving it, you know, for Alzheimer's and breast cancer and CFPD. And I agree that you really have to do a much better job of educating people what it means.

When the HD test first came out, I mean, somebody called me -- because everyone kind of knew that, you know, it could harm your insurance. So someone got tested through their GP, and she called me up on the phone. We're not supposed to give information on the phone. And that's, you know, also a violation of the guidelines.

But she said, well, I just got this envelope from my doctor and he said, well, I don't know what that means, but you better call somebody. He said, you have one big AL. I said, what do you mean, a big AL? Yeah, I got a big AL and a little AL. What does that mean? So I figure she was talking about alleles, you know? You had a big allele and a little allele, but the doctor hadn't a clue what was done.

So I think that we have to do much, much better just figuring

out, you know, what is this information. People do not understand risk. You can't tell them about risk or this is more of a risk or a less of risk. So how do we even begin to understand, you know, ourselves what this information means? And then it is an educable moment, you know, but only really, I think, if we control the flow.

If it's all out there so that we don't know -- you know, people spit parties and then they send in their, you know, spit to 23andMe, and God only knows. And people come back and say, What is this? I didn't understand what they were saying. And these are employers and scientists, and they still don't understand what's going on. So I think we have to, you know, pull it back and really kind of understand.

DR. MAHOWALD: Thanks a lot, Nancy. Some people agree completely that Huntington's testing has had an awful, awful history, and if we go back far enough, an unpredictable history in terms of its results. But they may view Huntington's as a very different, more serious disease than others that could be tested.

Now, all of the really totally nonmedical things that could be tested for and all of the ways in which companies may distort and clinicians may not be sufficiently knowledgeable about aside, putting those things aside, how do you counter the criticism that to deny the option of buying genetic tests for oneself in many, many other cases, say, breast cancer screening, for example, to deny that option to people, which could and has in

some cases led to preventive behaviors, is not paternalistic?

DR. WEXLER: Well, I would say that the Huntington's disease test experience actually, given how serious it is, given how careful we have been, I think there could've been a lot more catastrophes. There are probably a lot of catastrophes that we don't know about. But the fact that, you know, just 10 percent of people worldwide are taking it, they're really with their -- You know, I think all of us thought, oh, of course we'd want to know. But then we actually thought, well, what is it you're going to find out? You know, a lot of people said, no, this is not worth it.

I guess my feeling is that, as a woman, if I want to know if I'm going to have breast cancer, I would like to go to a doctor. I would like to talk to a doctor and say, Can you -- you know, I'm Jewish. You know, I hear that I have a higher risk of that presence. Can you talk to me about the BRCA2 gene? Can you talk to me about testing? What does it mean?

The fact is, I think the problem really is -- I think, frankly, it's just as bad -- not just, it's extremely bad to find out that you're going to get breast cancer, and if you find out, you know, all alone, downloading it on the web, this is not good news. And especially, you know, if you have kids and you're working, you don't have a doctor, you don't have health insurance, you can't afford medicine, what does that do to you? I think it's excruciatingly traumatic.

And getting some little information on the web, they don't give

you a person or, if you get a person, you have to pay \$5,000 more, and God only knows what the person or counselor says.

You know, colon cancer. Why is that good news? You know, these are things we can do. There are things we could do preventively. But if it were at all possible, I would like to be able to train -- you know, you could train genetic counselors, nurses, healthcare advocates, hospitals. There are a lot more people that could be part of a healthcare network -- you know, more available because I don't think any of these diseases -- frankly, I think that most people don't understand the information and don't know what to do with it when they get it. So why not try at least have that be a front door to a healthcare setting and a doctor to be able to actually discuss it and do the test and give the results?

DR. WATERSON: Okay, thank you very much. I'd like to thank all of the speakers this morning for their very informative talks.

I think we'll take a 10-minute break, and we'll convene back here at about 10:50.

(Off the record.)

(On the record.)

DR. WATERSON: It's now about 10:53. I would like to resume the Panel meeting.

We'll continue with the guest speaker portion of the meeting. Again, each presenter will have approximately 25 minutes to present and five

minutes to answer questions from the Panel. The first speaker is going to be Dr. Daniel Vorhaus. Dr. Vorhaus is already at the podium. Just state your name and your affiliation for the record.

MR. VORHAUS: Sure. Thank you very much. My name is Dan Vorhaus. I'm an attorney. I also have a master's in bioethics. I'm an attorney with Robinson, Bradshaw & Hinson, a law firm based in North Carolina and based in New York. And I am also the editor of the *Genomics Law Report*, an ELSI advisor to the Personal Genomes Project and Genomes Unzipped, among other research projects, and I work as legal counsel with several DTC companies and other companies in the much broader genetic testing and personal genomics space as well.

So by way of disclosure, I just want to make it all very clear to the Panel -- and please, please take that with whatever grain of salt is appropriate, but I'm going to do my best to present a balanced overview of where we are right now with DTC genetic testing and help us, as the title of the talk says, clear a path forward for DTC oversight.

So my first slide just out there. I know we don't have a webcast, but these slides will all be available and feel free to use them. Keeping with the openness theme of a number of the research groups I represent, this is something that I think is important, to make sure the information gets out there.

Okay. So I want to start with why we're here. And we had a

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great talk from Dr. Mansfield earlier, and so I'm not going to belabor this point. I am going to thank NHGRI for making this slide available and agreeing to update it. It saves me the trouble of having to update this every time I talk because, as you can see, the line just keeps dropping closer and closer to zero.

But really, this is the fundamental reason why we are now here talking about something like direct-to-consumer genetic testing, when a decade ago, when we were publishing the draft of the human genome sequence, we were talking in terms of more than a decade to get that data and billions of dollars, and now we've got whole genome sequencing, we've got DTC genotyping for hundreds of dollars, and that's what's really enabled this.

But why are we really here today at this specific meeting? It's the explosion of personal genomics and all of the related developments, particularly in the last couple of years. You can trace it back to 2007, but it's really picked up even just in the last year or so. An entirely incomplete sampling of some of the things that have been on my radar screen, on our radar screens, over the past year, I want to highlight one just very briefly.

You'll see My Gene Profile on here, up sort of near the top, and we actually heard a lot about them in the last talk, and I'm not going to focus on that too much. I just want to point out that, as far as DTC tests go, I would probably take issues with the previous characterization of this company. I

don't think it's at all representative of the companies that are out there right now. It's a Singapore-based company. It's basically a pure scam. The claims that they make are not supported by any kind of evidence, scientific or otherwise.

And so I think I want to make sure that the Panel is aware that this is not really the state of the DTC industry. It's not really what we're here to talk about. In a way it is. We need to make sure that pure scams in genetic testing are off the market just as they need to be off the market in used car sales and any other commercial marketplace, But, again, I would say, not representative of DTC genetic testing. But all of these issues have fed into the need to call this meeting here today and to discuss with you all and with the FDA what we should be doing about DTC genetic testing.

But I think we can focus our discussion much more narrowly. We've been given a charge by the FDA about the specific types of DTC genetic tests that we're looking at, and I think, even within that fairly narrow charge, we can focus in even more closely on some of the elements that the FDA would really like to consider here.

So we're talking about within this broad landscape of personal genomics and even within DTC. It's some pretty simple math. We're looking a very narrow subset, clinical genetic tests -- so clinical is very important -- with DTC marketing and other direct-to-consumer elements that we're going to talk about, and with no clinician involvement. That's the other clearly key

criteria here for this particular set of tests that we're talking about, and what are the issues that this combination of factors produces?

So a lot of text on this slide, but I actually think it's important and I know it's going to be tough for people in the audience to read it. Again, all of this is available.

But I think I just want to point out, what could DTC mean?

There are a number of different areas where we're looking at a genetic test, and we're asking, Is there direct marketing of the test or is it being marketed to laboratories, to physicians, to clinicians? Is there direct ordering of the test or is it done by a clinician with a prescription? Is there direct payment or is it reimbursable by insurers or other healthcare providers?

And then we talk about the data that comes back from the test. Is it returned directly to the individuals or is it mediated? Is that process mediated by a clinician, a doctor, a genetic counselor, somebody else with training in genetic testing?

And what kind of interpretation is afforded that data? Is it just raw data that comes back with no interpretation? Does it come back with you can buy an added interpretation, if you want, or does it come back with a much more detailed interpretation of the data? And then, who is providing that interpretation? Again, is it an actual person with training or, increasingly, as we're seeing, is it software driven or entirely software based?

Other, I think, additional factors that we want to consider

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because I do think they're material to the analysis, the purpose of the testing. Is it primarily clinical in nature? Again, we've seen that's the FDA's real focus.

But there are also DTC models or elements of DTC companies that are really focused on research. And I think we'll probably hear more over the next two days from companies that have been looking at the DTC approach as a way to develop novel research models, build large participant datasets that can be quite useful in research.

And then the commercial aspects of these companies, too. I think nonprofit, direct-to-consumer or direct-to-individual genetic testing has a very different aura about it than for-profit, and we're seeing some of both at this stage.

And then the mechanism of ordering, too. We saw quite a bit of consternation when Pathway Genomics put their tests or attempted to put their tests on Walgreens' shelves. That seemed to engender a bit more concern than making those tests available online for people that go seek them out at various websites. So there's the mode of delivery. Does the mechanism of delivery matter? And I think probably it does.

So those are all the different elements that we might need to consider when we're talking about DTC. But what does DTC mean to the FDA? Let's go back to this narrow charge. Okay, we know it has to be clinical. We know it needs to be marketed directly to consumers. We know that the consumer needs to be able to order the test directly without a prescription,

without getting a clinician involved, and we know that they need to receive the results directly, again, without a clinician involved.

What we don't necessarily know, does the identity of the payer matter? Does the mode and the method of interpretation matter? Is that subsumed in this category of data receipt? Are we tackling that all as one issue? Again, does the mechanism of ordering and data return matter?

So one challenge or one question I would put to both the Panel and to the FDA is, as we move forward, to try and be as clear and precise as possible when saying this is the type of clinical direct-to-consumer genetic tests that we are concerned about, that we think needs some additional oversight. Because once we hone in on that particular type of test, it tells us, it tells consumers, it tells companies and their investors, here is the type of test that concerns the FDA. Here is the type of test that is going to merit this oversight, whatever it's going to be. And also, by extension, here are the types of tests that fall outside of this model, that we are not as concerned about, that don't seem to us to be as risky and maybe admit of other business models or other approaches to testing. So precision here is, I think, particularly important.

So with that said, what is the single question that we have to answer today, starting at the big personal genomics landscape and going all the way down to direct-to-consumer genetic testing? I can tell you what it's not. It's not do we need to regulate personal genomics? That's not what

we're asking here today, even though it's an important question. And it's not do we need to regulate genetic testing? And it's not even do we need to regulate DTC genetic testing?

The question is do we need to regulate clinical DTC genetic testing when it has all of these other specific elements involved in the process? So direct marketing, direct ordering, data interpretation directly to -- and received directly to the consumer. That's the question that we're talking about here today, and I think framing that question very specifically and narrowly is going to be important for developing appropriate oversight of this area.

So in that same vein, we know what the question is. I want to just say a few words about what the questions are not because they come up a lot. They've already come up in some of the presentations. I think we'll hear more about some of these tangential issues. They've certainly appeared already in the public comments that were submitted.

Things that we're not talking about today, even though they're important issues, important questions, But, again not the focus here, laboratory developed tests, including the relationship of DTC tests to LDTs -- and we heard a little bit about that from Dr. Mansfield earlier, and I think many of us are looking forward to hearing more. Non-clinical DTC genetic tests, so genealogy probably the most popular type of DTC on the market right now. Not up for discussion here today. I don't think anybody's too

worried about people diving into that type of information, at least when it's limited to genealogical information.

If you want to go out and purchase myredhairgene.com's test, you can. I'm not sure for what purpose you'd be buying it, but people can spend their money in all kinds of interesting ways, I've found.

Other things that are not the focus here today, a number of the really interesting and important ELSI issues, ethical, legal and social issues around genetic testing that generate all kinds of interest, things like genetic privacy, acceptable uses of genetic testing outside of the DTC context, unacceptable uses, again outside of the DTC context, things like genetic discrimination. All of these things are very important issues, But, again not specific to -- they're not unique to clinical DTC genetic testing as we're talking about it here today.

And then there's the big, big non-question, I think, which is, does clinical DTC genetic testing need some additional oversight? I think the consensus -- I think we have consensus at least from everybody that I've talked to both inside and outside of industry and government, consumers as well, people that purchase these tests. I think everybody agrees that we need some additional oversight. I think even at a minimum you see examples like My Gene Profile, pure scams that nobody wants to see out on the market. They provide no value and they distract from what can actually be useful and valuable in this area.

So I don't think we're talking about whether there should be any additional oversight. I think the question that we're talking about is what kind of oversight should we have, and how do we provide effective oversight without stifling innovation in personal genomics and personalized medicine? So that's, I think, the focus of this discussion.

So we've heard a couple times already the three primary questions that FDA has put to the Panel and to the rest of us in the audience here today, what we're supposed to be addressing. The issue of clinician involvement obviously number one, also the risk of misunderstood tests or incorrect tests, and then appropriate evidentiary standards.

But there are also two, I think, or a few really important points that we also need to be considering. We heard about them a bit from Dr. Mansfield, again, in her talk this morning, and I think that was very helpful. But as we look at the oversight of DTC genetic testing, it's important to look not only at the landscape as it is today, but as it is almost certain to evolve over the next couple years. And that involves really paying attention to the incorporation of whole genome sequencing into the direct-to-consumer marketplace because that's coming. We've had DTC genetic testing for about three and a half years right now, and I'd be willing to wager that in three and a half years from now, the majority of DTC testing is going to involve whole genome sequencing to a degree.

Now, not everybody is going to probably have a whole genome

sequence at that point, but it's going to be substantial enough that it's going to be a major part of the DTC industry and something that we need to be thinking about here today so that whatever comes out of this meeting and future meetings is appropriately designed to deal with that.

I think there are two main distinctions that whole genome sequencing are really going to bring into play. The first is that it's going to make it increasingly difficult to distinguish between clinical and non-clinical tests. When you get back six billion base pairs, it's going to be difficult to say, well, here are the ones that we think are clinical and here are the ones that we think are non-clinical, especially when the biggest category is going to be here are the ones that we don't really know what they mean yet. So that's going to be, I think, a major distinction from where we are right now.

And it's also going to completely divorce -- this is something that's already happened, but it's going to completely divorce the process of testing, on the one hand, so spitting into a saliva collection tube and sending it off to a lab to be genotyped, and interpretation, on the other hand.

So when you get to a point where people routinely have their whole genome sequence data on hand, stored on a USB drive or up in the clouds somewhere, you're no longer going to need to have the testing and the interpretation combined together in one product.

So you'll have pure interpretation services. You can think of it a lot like an iPhone. You buy the iPhone once. You buy the hardware once.

And then after that you've got -- you go the Apple iStore and you've got any number of different apps that you can buy for your phone, and you can get games, you can get business apps, you can get medical apps, you can get all of these different things.

And looking forward to the future of DTC genetic testing in an era of whole genome sequencing, I think it's going to look a lot like that. You'll have the genome, that'll be your core platform, and on that top of that, you're going to be able to overlay any number of different interpretations, analyses, DTC-type products. Again, whatever type of oversight we're looking at here, it's got to be prepared for that kind of landscape, not just the landscape that we have today.

So with that said, and as we start to think about what the appropriate form of DTC oversight might be, I do think it's helpful that we have a number of areas of clear, common ground here. I think there's widespread consensus that we need clear scientific evidentiary standards. That's point number three that the FDA asked us to address. Now, I'm not sure that everybody agrees exactly what those standards should be, and that's, I think, a big portion of what we're going to hopefully be discussing through the rest of these two days and beyond, but I think there's consensus that it needs to be there.

I also think that access to raw genomic and genetic data is fairly well agreed upon from Francis Collins on down within the governmental

leadership. I've not heard or seen anything that suggests that people are really talking about trying to prevent people access to their raw genetic data. It's the interpretations that are imposed over top of that data and the way the data is used and marketed to individuals and whether or not there's a clinician involved that I think are the issues that we're discussing, but not the access to the raw data.

I also think that there's a strong and possibly universal desire for greater transparency in this area. Again, hearkening back to the example of something like My Gene Profile or My Gene Test, that's the type of product that's out there in the DTC landscape that I think everybody that's thinking about this and seriously looking at how to improve what we're doing in the DTC area would like to shine a bright light on and say, Look, don't fall for this. This is a scam.

And so when we talk about transparency -- and we heard Dr. Mansfield say just how difficult it is to figure out what's out there in the DTC industry right now -- that's what we mean. There's a strong consensus to gather more data about what types of products, what types of tests are out there, how they're being marketed and how they're being used. And then what we do with that information and how we choose to regulate based on that information, I think there's plenty of room for discussion. But the need to collect that information, the need to have greater transparency into what's going on in the DTC industry, I think, is fairly widely agreed upon.

And, again, Dr. Hogarth mentioned this earlier, but we're talking about oversight, not necessarily prescriptions. So I don't think, again, anybody wants to have completely hands off, and I don't think anybody's saying let's ban everything. Well, I don't think very many people, I should say, based on what we've heard. But I don't think very many people are saying let's just ban everything that involves sending genetic information to consumers. The question is how to do it responsibly, again, to preserve and protect public health, while also balancing that against the need for access to data for innovation and concerns like that.

Okay. So what are our contested grounds when we're talking about DTC oversight? So I think the first issue that the FDA posed to us, the use of clinical DTC testing without clinician oversight, I think this is probably the most controversial area. I think, from talking to people, from reading what commentators write in this area, from talking to companies, this is the area that gets people farthest apart from each other. Do I need to have some kind of clinical involvement before I'm allowed to access my genetic information? And what does that process look like?

We saw, for those who've had a chance to look at the public comments, the American Medical Association laid out their concern, this fear that direct-to-consumer testing will have a significant adverse impact on consumers and undermine the physician-patient relationship.

So as we think about this, I think we've got to ask a couple of

key questions. First and foremost, is interposing a clinician a realistic possibility today for all DTC testing? And as you can see, I've presented a little brief, you know, data about this on this slide, and there's plenty more out there.

But I think there's a real question about whether or not we have enough people trained in this area right now to meet the demand of the entire DTC field if we were to say everybody who wants to have this test needs to first have a consultation with a clinical geneticist or with a genetic counselor or somebody like that, keeping in mind that routing this through your general practitioner, at least today, is maybe not going to be the right option just because there are probably many consumers out there of these products that know more about the underlying science and basically the quality of the information they're getting than their doctors do at this point.

And so I think there's a broadly recognized need to improve the number of people with training in this background to improve the ability of doctors to handle this information as it becomes more and more important in their practices. But I think that's a primary question.

And then the big one is who should decide when and whether a clinical counselor is required. Should that be decided by regulators, by the FDA, based on the nature of the test? Should it be decided by clinicians, for instance, based on what they think is indicated? Or should it be decided by consumers? You know, let me tell you when I think I need to have a doctor or

have a genetic counselor involved in understanding this because I don't think I get it.

So related to that point is FDA's issue number two, which is this danger of incorrect or misunderstood test results. So I think one of the fears in letting consumers say, well, I'll tell you when I need to have a doctor involved in this process, is this fear that consumers maybe are not appropriately trained or able to really understand when they're missing something, when the test might be wrong, when they're not understanding the results that are being reported to them, when they might be mistaken, and the harmful types of outcomes that could result from that.

And the key question here is we're really still digging into this. I don't think, other than a few anecdotal accounts, we don't really have any hard data of individual consumers who have been harmed by direct-to-consumer genetic testing under most definitions of what we would think of when we talk about harm. But we just don't have a lot of data, period. And we've got some that's now starting to trickle in, about how consumers and how individuals react and interpret DTC genetic testing. And I know we're going to hear more about that today from some of the other speakers, so I'm not going to go too deeply into that, other than to say that I think the results so far seem to indicate that people are generally fairly satisfied with the process of DTC genetic testing, and the rate or the risk of misinterpretation of errors, of harm resulting from it, has yet to be shown with data.

Now, again, keeping in mind that we're dealing with very limited data, and I think no matter what happens going forward, it's going to be important to continue gathering that data to figure out exactly how people are responding to this information.

Let's see. So a few other additional issues that I think we need to be sure to consider. The role of utility and oversight here, so clinical utility versus personal utility. DTC genetic testing is a source of clinician and consumer information and education, especially in the current context of federal budget cuts.

When we talk about getting this information out in a meaningful way, in an instructive, helpful way to individuals, whether they're patients or clinicians, I think we at least have to take a close look at the ways in which DTC companies are doing this, and some of them doing it quite effectively, and look at that as a possible upside of DTC genetic testing.

And then we talked about multiplex whole genome tests. Again, I can't overemphasize that enough, the importance of designing oversight with that future in mind because it is coming.

And then the other thing that I think is very important is coordination. Again, we brought it in so narrowly at the beginning to talk about just how specific this notion of clinical DTC genetic testing is, but that comes in the context of a much broader personal genomics landscape. There are all kinds of regulatory and legislative issues happening at the federal

government level, at the state level, at the international level, as we heard from Dr. Hogarth, and the only way that this works is with close coordination.

And, again, thinking about how are we building out a structure for the future of personalized medicine that works? So we heard from FDA Commissioner Hamburg and NIH Director Francis Collins last summer in the *New England Journal of Medicine*. I'm sure most of you people saw "The Path to Personalized Medicine." If we're going to get that path, we need to have a consistent, a coherent regulatory and legislative oversight structure across the personalized medicine landscape. We can't be too myopic in our regulation and in our focus here, even though that's in some ways what we're being asked to do here today.

So, finally, what's coming next? Is it should we have transparency? Should we have more direct regulations? Should we have both? I think there are good, strong arguments on both sides. Again, in the interest of trying to not play too much of an advocate's role here, I just lay these out there as, I think, two options that I think can be alternatives but also complementary to each other.

So thinking about oversight, again, I think no matter what happens, this increased transparency is going to be important. So supporting efforts like NIH's genetic testing registry, which is still in the works and there's been some discussion about, well, should that be voluntary? Should that be mandatory? Should DTC companies be required to participate in that

so consumers have a place to go?

And the real tensions here are, I think, twofold. One is innovation tensions of balancing public health concerns and concerns for consumer safety against innovation and concerns for consumer access and desire for direct access. And then, again, this fundamental tension of interposing clinical guidance into the process of DTC genetic testing as opposed to safeguarding individual autonomy and giving people the ability to access that information on their own.

So I think that about wraps up my time. I want to leave some time for questions for the Panel, but we can get to those now or afterwards. I'm always available.

DR. WATERSON: Dr. D'Agostino.

DR. D'AGOSTINO: Yeah. Thank you for the presentation, it was very interesting. I'm confused in terms of did you leave out a very important aspect because you assumed it was going to be done whether it's direct or FDA involvement or medical involvement? But what about the validity of these tests? I mean, it's not so much that you interpret the results, but are the results correct?

I mean, if it's done on -- if your odds ratio isn't based on a case control versus a cohort study, if the data you're getting doesn't really add to just some clinical parameters and so forth, are you assuming that that's going to be done whether it's direct or not direct? I think that we should be

keeping that clear in mind, that some of these procedures aren't very useful.

MR. VORHAUS: Right. I think that's an important point, and in talking about the common ground, I agree. I think everybody or, again, most people aren't qualified, but most people would say that establishing validity, so both analytical validity and clinical validity, is paramount.

And, again, that's true when we're talking about any kind of genetic test. That's not something that's unique to DTC genetic testing, and arguably, it's much more important when we're talking about non-DTC. We're talking about pure clinical genetic testing, where something is going to straight to a doctor, and it becomes even more important to be sure that the tests that are going on the market there are analytically valid, clinically valid.

And so this is a conversation that I think is happening both inside this meeting and then much more broadly. I'm not a scientist, so I'm not really the right person to weigh in on exactly what that standard of validity should be, but it's clear that we need to come up with a clearer standard for how we determine that.

DR. SHAMBUREK: Yeah, your very first slide, you know, it's the one that has already shown how we've cut the cost down and we can make G's and C's and T's. However, the second slide should really be the opposite one, which was logarithmically going up, of people to interpret that information.

And you can make a lot of parts, but you have to make the car,

and we don't have those blueprints, and we're already spewing how good we can make the parts. But I think we have to be very concerned that if this gets out there, it can be very easily misinterpreted.

And you talk about the future. What's going to happen when someone gets the first generation platform and now the next one has 10,000 more, those risks and other assessments? You're going to have to buy the next one.

So I think there is a great need in the industry and the scientific community to realize that we've really cut costs in making G's and C's, but we don't -- right now, anyone who's doing genomic-wide or whole exon, whole genomics, really is overwhelmed. And I think we do need industry involved in everything, but I think we don't want to jump ahead of the scientific information.

MR. VORHAUS: I think that's exactly right, and there's no question that the rate of decline in the cost of interpreting all of this data is actually as you say, it's going the other direction as we get more and more of it, and it's probably going to continue trending in that direction for quite some time. Possibly indefinitely. But, again, I think that point is exactly right. I also think it's a point that is much larger than direct-to-consumer genetic testing. It is an issue that NIH is grappling right now with research grants, funding, whole exon, whole genome sequencing, and it's something that we need to be looking at across the genetic testing landscape, not just in DTC.

And, again, I think that there are certainly ways in which DTC companies can help researchers help the government present that information and do a good job of saying here's what we understand, here's what we don't understand, again, going back to making sure that we first have these standards for clinical and analytical validity.

DR. LUBIN: One of the key issues in making decisions is the question of what makes a good claim, and whenever you have a product, you're going to make a claim for the purpose that that product serves. And where I think we need to come to common ground on is, you know, where is sort of the intersection and how do we deal with it between what is stated as a claim, what's an implied claim, and how do we come to terms in using that information to make a decision about what's the appropriate oversight for a particular product? How do you see this sort of working its way out?

MR. VORHAUS: Well, I think that's a great, great point. And when you talk about claims, we're talking here about medical claims, obviously, and clinical claims, and that's where we have to get again into this issue of clinical validity and establishing those standards.

But we're also doing more than that, especially now here we are talking about something that's very specific to DTC, we're talking about advertising claims, we're talking about marketing claims, both expressed and implied, and this is an area in particular, I think, FDA doesn't need to shoulder the burden alone. We have other regulatory agencies, most notably the

Federal Trade Commission, who are tasked with monitoring, regulating, preventing false and misleading claims.

And I think when we talk about transparency, I think that's one way in which we can bring other agencies into the picture and get real enforcement of some of these regulations, not necessarily through the FDA channel but through other consumer-focused channels.

DR. HERSCH: In talking about benefits, specifically for DTC, you mentioned autonomy, you mentioned innovation, but it's hard -- I'm interested in what your vision is of how -- what the benefits are for personal health information derived specifically by DTC and how that would be different from other ways of deriving benefit.

MR. VORHAUS: Well, I think we're still -- I mean, there would be a couple ways to respond to that question. One is that I think it varies tremendously by individuals. So for some people, getting this kind of personal involvement and personal access to their information appears to be quite powerful as far as motivating changes in lifestyle, changes in behavior, in addition to the informational content. For some people it appears to have not much effect at all, and it's more of a curiosity, I'd say.

Speaking personally now, I fall into that category, at least at the moment. I have been genotyped a couple of times, and it's mostly informational curiosity for me in many respects.

DR. HERSCH: But given the odds ratios associated with a vast

majority of the information, there's a lot of activity, expense, thoughts, life changes that are being based upon pretty skimpy information and those aren't -- those have a cost, whether they're good for you or not.

MR. VORHAUS: Well, again, I mean now I think we get into the question of utility, probably, to a degree. So I think what you're asking is, given odds ratios, given the uncertain nature of many of these associations, why would anybody bother doing this? Why should we maybe let them spend their money for it?

I guess you can certainly make the argument that people should be allowed to spend their money on just about anything they want, as long as it doesn't harm them, and so that's where we get back to this issue of is this harmful? And that being maybe the more important question than what is the benefit? Just because we don't think something is beneficial doesn't necessarily mean it needs to be pulled from the marketplace.

But also I think it's important to consider both clinical utility, which is obviously an important factor, but also this concept of personal utility, which is sometimes fairly nebulously defined but, I also think, important to consider.

I think Alzheimer's testing would be a good example of that, where it's not -- now we're backing away from the DTC context, necessarily. But this is something where you don't have clear clinical interventions, but yet people still find them. We've seen data from the REVEAL study at Boston

University. People can still find that information very useful to them in thinking about how to go forward with planning their lives, their families and their affairs, that sort of thing.

So there's more than one way to think about utility, I think, in a context of genetic testing, and that includes DTC genetic testing.

DR. WATERSON: Thank you very much, Dr. Vorhaus.

MR. VORHAUS: My pleasure.

DR. WATERSON: We'll move on. The next speaker is Colleen McBride.

DR. McBRIDE: I can state my name and my affiliation. I'm Colleen McBride, and I'm with the National Human Genome Research Institute.

So I'm here this morning -- and thank you very much for the invitation to speak today -- to talk about a single study and its implications for our task at hand, direct access to genetic testing. And I'm going to basically focus on three take-home messages that I think the Multiplex Initiative brings to this conversation.

The first is that, in our experience in the Multiplex Initiative, there was considerable self-selection in who showed up to seek genetic testing, and with that assumption as a background, our use of effective communication strategies, that is, evidence-based communication strategies for conveying health information, that with that information those individuals

were able to make an informed decision about whether or not they wanted to be tested and that, again, iteratively, among those who -- the self-selected group, with the proper information provided, that those testers were able to understand the limits of the test feedback.

My remarks today are going to be organized first to just give you a very brief overview of the Multiplex Initiative, and then I'm just going to highlight some data from that study to support each of those take-home messages.

So first off, the overarching aims of the Multiplex Initiative, which was initiated about five years ago in anticipation of the DTC marketing that we were expecting on the horizon, was to identify a population-based sample, that is, a sample in which we knew the denominator so we could know a lot about the individuals who were tested and weren't, and under ideal dissemination conditions. Ideal, again, meaning that we had eliminated as many barriers to access as possible and had provided adequate pros and cons information about the testing.

Some very basic questions: How many people would consider and be interested in testing? What factors would be associated with their interest in testing? And, then, how would individuals respond to the test results, with respect to emotional responses and their understanding and appreciation of the limitations of the test results?

Our study design was that we worked with a clinical site, the

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Henry Ford Health System in Detroit. We selected that site because it was part of a large consortium of health maintenance organizations and had a very representative demographic breadth in its group. We worked with the Group Health Cooperative, another HMO, to do all of our surveying.

This was a population-based sample, in that we selected our individuals from the enrollment records of Henry Ford Health System, after some pre-selection for some of the health conditions, to target healthy adults as we imagined that the DTC companies would be doing themselves. These adults were specified to be 25 to 40 and they could not have any of the health conditions on the test battery.

So we also wanted to make sure that we touched a representative sample of patients in the Henry Ford Health System. So in order to do that, we had to over-sample groups that are typically underrepresented in health research. Those are African-Americans, men, and those who have low socioeconomic status, and given the enrollment rolls and using census data, we were able to over-sample those groups. And you can see here the sampling strategy, which adds up to 100, representing the groups that were over-sampled.

So our cascade of study methods were that we identified this sample from the Henry Ford enrollment rolls. We attempted a telephone baseline survey with about 6,000 of those enrollees as our sampling frame. We provided, then, those individuals who were eligible, adults 25 to 40 who

didn't have the health conditions and had some other eligibility criteria that they met, we provided them access to a website that they could visit to read about the test and decide whether they wanted to be tested or not.

Those individuals who went to the website, read through the information and decided that they wanted to be tested, were then scheduled for a clinical visit and had a blood draw and some additional informed consent processes there. The individuals, about four months later, who were tested received their test results by mail with a telephone follow-up from a research educator to discuss the test results, with the primary purpose to make sure that these individuals understood what the test told them and what the test did not tell them. And then about three months after receiving their test results, we did another telephone survey follow-up with just those individuals who had elected to test.

This is a picture of the brochure that we used, and I just point out here that while they could visit the website, they also could call a toll-free number to complete all of these, the decision and so forth, all by telephone. No one elected to do that.

Our test we had to develop because, again, this was five years ago -- I won't describe to you the detailed evidence-based process that we went through. It's published and the reference is here for you. But we identified eight common health conditions and 15 genetic variants within those health conditions that met the criteria.

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The eight common health conditions were selected because they have a strong public health impact, they were all adult onset, and they were all preventable. We eliminated any genetic variances that had -- were also associated with any diseases or health conditions that were not preventable or adult onset. So thus we wound up with a fairly small number of genetic variants and health conditions.

This is a picture of the test feedback booklet that individuals got. They had their results on one side and then they had several -- some supplemental information in writing that we attended to literacy requirements to make sure that this information was presented in the most understandable formats. You can see here that much of this was about the caveats, the limitations of the test results with respect to prediction, certainty, and so forth.

This is the inside of the test result booklet, just showing you that, for each of the health conditions, the individual was told whether or not they had a risk aversion for the gene that fell within that health condition. And, again, they were directed and you can see -- if you are close up, you can see in red that they were also directed back to the website, where there was detailed information about each of the common health conditions and each of the genetic variants so that they could remind themselves.

This is our denominator. We wound up surveying 1959 patients of Henry Ford. I really show this to illustrate that this was not a worried well

sample. This was we were successful in recruiting more than half African-Americans in the sample, about half were men, and you can see that only 23 percent of the sample rated their health as excellent, even though they were 25 to 40. Overall, 35 percent were obese, 28 percent were current smokers, and the majority of these patients had a health behavior or a health habit that they wanted to change.

I think it's also noteworthy, in the last two lines that you see, that overall these individuals rated their confidence to understand genetics as 5.7 on a 7-point scale,. So that's a relatively high self-rating, that they were confident that they could understand genetics, and it was substantially lower than their confidence that they could deal with the healthcare delivery system. Now, you could argue that they've probably had a lot more experience with a healthcare delivery system than they had with genetics and, therefore, they may have downwardly adjusted their confidence.

So in terms of our take-home message, our first take-home message about the fact that there's considerable self-selection that's going on and who shows up for these tests, we first looked at that by social group, and what you see here is that African-Americans were unlikely or less likely at each stage to opt to do the baseline survey, to visit the website to even consider testing, or to be tested once they did visit the website.

Likewise we saw that those who lived in neighborhoods that were characterized by a low education level, because we used census data to

get at our education, that those had less education were also more likely to opt out of the survey and the website. But once they showed up at the website, they were equally likely to get tested. And men were less likely to participate in our baseline survey but participated equally to women in all of the other steps.

So I think also, in terms of thinking about self-selection, just reminding you here of our denominator of 1959, that only 612 of those just under 2,000 went to the website to consider testing at all, which is 31 percent of our initial baseline sample. And then if you trickle down to who actually showed up at the clinic to have a blood draw to get the test, only 14 percent of that denominator opted for testing.

When we look at the predictors of who it was that showed up to consider testing at all, besides the demographic characteristics I just mentioned, the race and education, access to the Internet, we had fairly high levels of access to the Internet in the sample, a relatively young sample. But the more time that these individuals spent on the Internet, the more likely they were to log on to consider testing, and the more that they perceived learning about genetics to be important, the more likely they were to log on to consider testing.

With respect to the predictors that were associated with who got tested, what you can see here is that we carry on with this theme of self-selection. The individuals who perceived these health conditions, these

common health conditions, to be severe, the more severe, in fact, they perceived these health conditions to be, the less likely they were to seek testing.

The more competent that they were that they could understand what the test -- understand genetics, the more likely they were to seek testing. The more important they thought it was that an individual should be learning about genetics, the more likely they were to get tested. And the more they wanted to change their health habits, the more likely they were to get tested.

So each step of the game we're seeing individuals who are thinking of themselves as wanting this kind of information, not going to be particularly worried about it, are the ones that are showing up.

So in speaking to our take-home message two, which was that if we use best practices of health communications and risk communications, that people can understand this and can engage with this information. I'm highlighting data from our website.

So the individual showed up at the website and could review up to, what is it, 12, 29 pages of information online. Those test pages or those pages were divided into three categories: general information about the test, what was involved in having it done and what was done, about eight pages on -- a page for each of the health conditions, and then a page for each of the gene variants.

And what you can see here is, in comparing those who agree to test to those who did not agree to test, what we see is that individuals who wanted the test or ultimately got tested viewed more of the pages in each of those categories. So they engaged a bit more with the information. But I think what is really telling here is that, overall, they didn't read much of the information. And when you look at, in fact, some of the patterns of that, what you can see here is this is their engagement with the health condition pages and these health condition pages are listed in the order in which they appeared. So diabetes was the first page, osteoporosis, and so forth. And what you see is that the individuals, about just over 60 percent of the individuals looked at the diabetes page, but then didn't -- many didn't look any further than that.

So, in essence, which is a common a thing that we see, is that they got the gist of the information, in my mind, probably decided that this was information they already were pretty familiar with and didn't look on any further. Likewise what we see is the same kind of pattern with the gene variants, but the difference here is that probably this information was less familiar, so what you can see is that they looked at more pages in order to get the gist before they -- before we see it dropped off.

In terms of how the individuals viewed the content, what we can see is that, overall, there was fairly positive views of the information, seeing it as easy to understand, it was trustworthy, they were satisfied with

the amount of information and thought it was sufficient and felt that it was helpful in deciding whether or not to be tested, regardless of whether they chose to be tested or not. But what we did see is that the testers did seem to view -- those who wanted the test did seem to view the information more positively than those who did not test.

Also speaking to the take-home message number two is the idea of how engagement with the website influenced whether or not individuals thought the decision was easy or hard to make and whether or not they got tested. And what we see here is generally more engagement with the materials, more confidence that they would be able to understand genetics, and the more value that they placed on learning about genetics, the easier they thought it was to decide about testing and the more likely they were to decide to be tested.

So moving on to the take-home three, which is assuming in this cascade is that the individuals who show up actually can understand what it is they're being told. We compare here what is free and prompted recall of the test feedback. This data comes from the telephone call that the individuals who were tested had with a research educator after receiving their results.

The light blue bars are showing their unprompted response. We just asked them, What did you have? Which of the gene variants did you have and which of the health conditions? And the dark blue bar is us sort of suggesting, prompting them with, how about heart disease, how about

diabetes and so forth?

And what you see is that between 40 and 70 percent of the individuals across the health conditions could tell us unprompted what it was that they had a genetic variant for and for which health condition. And when we prompted them by reminding them of what the health conditions were, virtually everyone can tell us whether or not they had -- and accurately tell us whether or not they had the variant for that health condition.

In terms of emotional responses to the tests, we asked a series of -- from a popular psychological scale of emotions, to what extent they had felt each of these emotions since receiving their test results and strongly agree -- said that they were strongly endorsing that emotion. And what you can see here, which I think is striking, is that they're not overall feeling much of any emotions, not endorsing a very high level of emotions. But where they are endorsing emotions, those tend to be on the more positive side, which is feeling more hopeful and feeling relieved and, to a lesser extent, not feeling particularly nervous or afraid.

In terms of their ability to interpret the meaning of the test results and its caveats, which we thought that the -- we and our human subjects protections office thought was the most important, we had a very specific set of materials inside of our booklet, with all of the caveats to what this test could not tell them, and then we queried them after they received their test results to the extent to which each of these statements were true,

that they were not certain to get the disease, but there were other factors that influenced their risk for these common health conditions besides the genetics, that they would be able to lower their risk, it was possible to lower their risk, and that health habits were very important in determining risk for common health conditions.

And what you can see is that, across board, very strong endorsement of those statements, suggesting that they did understand that this was not -- these tests were limited in their ability to predict outcomes.

So I'll just remind you of where I started, the take-home messages being that there is a lot of self-selection going on in who shows up at the front door; that assuming that these individuals seem to rate themselves, even though this was a population-based and, I think, quite heterogeneous sample that was not overly educated or overly white or any of the other things that we've heard, that when we use effective communication strategies, that it does appear that these individuals felt that they had enough information to make an informed decision, and half of them decided not to test; and that among those who did decide to test, they do appear to have understood at least what we set as our watermark of what the most important caveats for them to understand, given that we focused on that and we used best practices to convey that information.

So I think, when we put this in context, how would we, based on this very limited experience, speak to what this means for deploying direct

access? And I think, based on this data, we would say that it may be okay if there's some effort to make sure that these communications of test results are presented, again, using best practices, pros and cons are presented in a format that is appropriate for a broad range of literacy groups, that, in fact, this can be done; that with public health-friendly support strategies such as the Internet and telephone support, telephone counseling, that we can provide the support that individuals need to make an informed decision about testing; and lastly that the public should -- and we emphasize should because we think it has two meanings here, but should be able to understand the limits of genetic testing.

And the reason we say should in this instance is that "should" in a sense that we are obliged, I think, to make sure that we're giving them the information that enables them to understand, and "should" also in the sense that they have the capacity to understand it.

A big "but" here is that Multiplex versus the current direct-access milieu is quite different, and it needs to be considered in your considerations today. The Multiplex test was free. That may have influenced who showed up at the door. But, as you saw, we still only had 14 percent that sought testing; that it included only 15 variants, and as we've heard this morning, the landscape is much larger than that, and those 15 variants were selected carefully to meet standards that would not be overly disturbing or might require extra efforts in the form of making sure that adequate support

was in place; and that the testers were all insured, with access to preventive healthcare services.

And that's the end of my comments. Thank you.

DR. WATERSON: Thank you very much.

DR. SHAMBUREK: A very nice study, and I think you met your goals, although I think this raises another important issue which wasn't the design here. But if we look, for instance, where you're looking for heart disease risks and you pick three variants, APOB, CETP, and NOS3, those don't cause the majority of cases of heart disease.

DR. McBRIDE: Right, right.

DR. SHAMBUREK: So if you have a 30-year-old who comes in, who, as a clinician, I know his father and grandfather died --

DR. McBRIDE: Right.

DR. SHAMBUREK: -- and now he's being -- he's hopeful because he has a low risk of developing heart disease. So I think that's a major issue that we're dealing with. So, you know, I think that's a potential limitation of testing where, if the next group did five, we don't know. Right now we're way ahead. But I think your issues of informing -- And, again, I don't think they always hear, know the limitations. I think they hear the information, you're low risk. But I think it's a very nice study.

DR. McBRIDE: Thank you.

DR. D'AGOSTINO: My comment and question is sort of a

follow-up on that, though I did raise my hand before you asked your question. When I look at these here, I mean, did you tell them that, for heart disease and blood pressure, you'd do better to take your blood pressure?

DR. McBRIDE: Yes. These folks didn't have any of those conditions. They were eliminated if they -- these were healthy adults.

DR. D'AGOSTINO: Yeah, I understand that. In terms of, you know, you give them this information on these genes, which may in fact mislead them in terms of what's going on and may in fact give very little information. They run to the diabetes page with a high rate, the highest rate, and family history, an oral glucose tolerance test would probably tell them all they really need.

DR. McBRIDE: And thank you for giving me the opportunity to say that because we did emphasize that genetics was only part of the story and that in order to have a full understanding of their health risks, that they should have a full family history done and that they should talk to their healthcare provider.

DR. TSONGALIS: So is there any data that would suggest enrollment would've been a lot higher if they didn't have to have blood drawn?

DR. McBRIDE: That's a really good question. At the time, it was a strong opinion that -- amongst our colleagues, that it needed to be blood to get adequate amounts of DNA. In hindsight, I mean, many of us argued for

doing buccal samples and were argued down on that account.

My guess is there would've been more. I think you also have to keep in mind, this was the first study and it went through a lot of review and was fairly critically -- it took us a year to get through the IRB. So I think that extra step of making -- putting a little more onus on a person to come in and make sure that the informed consent, that there was clear understanding, which we wouldn't have had to do with a buccal sample, I think the blood probably was good for that. But I'm sure it suppressed the uptake.

DR. WATERSON: I'd like to move on to the last speaker. Thank you very much for your talk.

Cinnamon Bloss.

DR. BLOSS: Good morning. I'm Cinnamon Bloss. I'm here from the Scripps Translational Science Institute in San Diego. And so it's a pleasure to be here today to have a chance to present some of our work at Scripps on consumer genome-wide testing, and in my presentation this morning, I'll be pretty much exclusively focusing on providing an overview of our Scripps Genomic Health Initiative, in particular, findings that are embodied in a recent publication at the beginning of this year.

So as we've heard this morning, GWAS findings are currently being leveraged by a number of companies to offer risk assessments based on common variants, and of course, part of the reason why we're here is that there's been so much debate regarding this practice.

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In general, people who are so often proponents -- and of course there's different definitions of different terms, as we've heard. But proponents of this practice essentially argue that access to this information has the potential to empower people to make, you know, lifestyle changes, health changes and so forth, and that they essentially have a right to this information.

Opponents, on the other hand, argue this is essentially a premature translation. There's the expense, there's the lack of information on clinical validity, clinical utility, and also a lack of data on consumer response.

And so essentially the last point there, the lack of data on consumer response, is where our study comes in, the Scripps Genomic Health Initiative, or SGHI, as we call it. This is a longitudinal cohort study of behavioral response to genome-wide risk testing for common diseases, and in particular we looked at response to testing with a current commercially available test, the Navigenics Health Compass. And our participants purchased this test at a subsidized rate. And I'll talk a little bit more about that in a minute.

And, again, our focus of this study, or at least of the findings that I'll be presenting today, are really on the consumer response or the impact. In particular we wanted to look at response in three particular areas, psychological impact, behavioral or kind of more lifestyle impact, which we

operationalize to mean diet and exercise changes, and then the clinical impact, which we operationalize to mean impact on health screening behaviors, intentions, and practices.

And, importantly, what we didn't assess and make no claims about is the Navigenics test itself, its validity, its utility, the markers that they use and so forth. So I just really want to emphasize that this is merely to look at how people responded to undergoing testing.

And our design was really based on studies, previously published studies that have looked at response to testing for single genes and conditions like BRCA testing for breast cancer and so forth. And I'll talk a little bit about our recruitment as well and our population because it's sort of clearly an important issue.

We started this study in October of 2008 and initially targeted Scripps Health employees, family members, and patients, and then, as the study progressed, eventually targeted employees of other health and technology companies. So this is a very limited sample. It's a selected sample as well. We don't have kind of a known denominator as the Multiplex Initiative does, which we just heard about.

And we kept our inclusion criteria purposely broad to try to facilitate an enrollment of as large a sample as possible, 18 years or older, valid e-mail address, since all our procedures were done online, which sort of mimics kind of the current way in which Navigenics does testing.

And then we had people provide a co-payment. The price ranged a bit, from 150 to 470, which was charged in the final months of the study. We had a lower price initially to try to encourage, again, early and large numbers of enrollment. At the time, the Navi test range was right around \$2,000. Of course, that price has changed since then.

This is just a schematic of our procedures which we -- throughout you'll see that we basically tried to kind of mimic the current way in which -- or at least in 2008, the way in which Navigenics was delivering their test. So we kept all our procedures online.

The participants were directed to Scripps landing page on the Navigenics website, where they had to read both our informed consent and also the Navigenics user agreement. They were also able to contact personnel at Scripps to pose any questions and so forth. They completed the consent -- if they chose to participate, they could complete the consent and provide their payment information, and then they completed our baseline health assessment, which I'll describe in a minute.

At that point or at some point after that, they would receive their personal genomic risk assessment from Navi online, and then 90 days following receipt of that information, we would initiate follow-up with them.

And everything I'm going to be showing you, all data that I'll be showing you, are based on our three-month follow-up. We're still in the process of conducting a 12-month follow-up, which we hope will enable us to

make -- to just get some more data on what are some of the more long-term effects of this type of testing.

So this slide is just mainly provided for background. These are some of the instruments that we use to assess our different domains. What I would point out here is that -- well, two things. First of all, there was sort of a tradeoff between sort of choosing appropriate well-validated instruments and needing to use instruments that were also brief. So there's definitely that sort of tradeoff here with our instruments.

Another thing I would just point out is in regards to health screening, since I'll be presenting some data there. We had two ways of looking at that, both actual screening tests that people completed post-testing, and also we asked them about their intention to complete different screening tests with greater frequency now that they had an undergone genomic risk testing. We further asked about sharing of results with a genetic counselor or their own personal physician. And, again, all of these are re-administered at our 12-month follow-up.

So, once again, just another reminder that we make no claims about the Health Compass itself, but just in order to better kind of put our findings in a context, I just want to show -- this is sort of a schematic of sort of the main page that people see when they first receive their results from Navigenics. There are various places that the consumer can sort of drill down and get more information about how risk is calculated, what variants are

used, and so forth.

But at the time of our study, our participants received results back for 23 conditions. I believe they've increased the number of conditions since then. And this box here -- each condition is shown in a box, and it's hard to see here.

And Navigenics also has several different ways that they kind of try to present risk, which means that you could kind of look at it as a function of their different presentations and could potentially see different results. And so you can see they provide what they call their estimated lifetime risk as opposed to the average lifetime risk for a person of the same gender. And then they also have a color coding scheme with orange indicating a higher level of risk than gray and so forth.

We also offered genetic counseling at no cost to our participants through Navigenics.

So we enrolled almost 5,000 individuals in our study and then obtained a good baseline on about 3600 people. Of those, 3400 viewed their results, and we obtained a good follow-up on 2,000 of those individuals, which is about a 56-percent response rate. Our average follow-up interval was also almost six months.

And this next table is also important. It represents the demographic characteristics of our cohort. So you can see, you know, there is a slightly greater percentage of females. Our average age was mid-40s, but

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we have quite a range, 19 to 85. But what I would stress is sort of the income and education level of our participants is very high. Also a large percentage of them are self-reported Caucasian.

So we certainly make no claims about our population sort of being representative of the general population. But we would probably assert that it is probably representative of the current population of consumers of these tests, given their expense and so forth.

So I'll now show you some results, again, looking at kind of the impact of testing changes between baseline and follow-up. And as I said, these findings were recently published earlier this year, and I believe they're listed on your bibliography.

So in the far left column our outcome domains are listed. The baseline and follow-up scores are then listed, and then finally a column indicating statistical significance. And I think what really strikes me about this table is sort of the general lack of impact of this testing in this particular cohort. What I would highlight in that regard is certainly what we're seeing with regards to anxiety, again, in this particular cohort, using this particular measure, just a lack of impact here.

The one area that we are seeing significant statistical significance, anyway, is with respect to what people were saying about what screening test they intended to complete after getting their results. So let me just back up a minute.

If you'll recall, we assessed actual screening behaviors and then also intended screening behaviors. There was no statistical significance with actual screening. This was merely asking people, Do you intend to get this test with greater frequency now? And that's what this finding represents.

And these graphs are also very small, but given kind of the emphasis on wanting to know issues related to harm with this test, I just wanted to also show -- this is available in the supplement of the paper that's on your reading list. But it essentially shows anxiety level of pre- and post-testing -- pre-testing is in blue, post-testing is in green -- as a function of different demographics. So the first one is income, education level, and then ethnicity. And what you can see is that, again, these are group effects. It doesn't rule out, you know, adverse events for certain individuals, certainly. But at a group level, again, what we're seeing is just kind of a lack of increase in anxiety with this measure in this cohort.

So moving on to health screening and away from kind of general changes pre- and post-testing, I'm now going to show you some data on actually looking at are there changes as a function of the actual risk assessments that were provided to our participants?

So list featured the screening that we asked about. The screening benefit for asymptomatic individuals is kind of commonly agreed upon in the medical community. We felt this was important to comment on, given the concern that this testing will kind of result in people going out and

wanting to get a lot of, you know, unnecessary medical testing.

And so the next column that I'm showing here is correlations with actual completion of screening tests and the genetic risk estimates provided, and what you can see is, basically, there isn't much in the way of actual screening behaviors post-testing. But when we look at what people said about what they intended to do in regards to screening, we see a lot of correlations with the genetic risk estimates provided.

So, for instance, the first is statistical significant finding in the intended completion category is just indicating that those at a higher risk for glaucoma were more likely to say, yes, I intend to get an eye exam with greater frequency.

This is also looking at correlations with genetic risk and psychological impact. Again, what we're seeing is, you know, given the multiple comparisons issues, just not a lot of impact. Just given that this is such a new field, and in the interest of kind of exploring the data, I am highlighting here the correlation with Alzheimer's disease, given that this was kind of one of the larger effect sizes that we saw. So this is in the domain of test-related distress. So how distressing was receiving the test results to the individual? And what we're seeing here is that people with a high risk for Alzheimer's reported slightly higher test-related distress.

And, again, in an effort to kind of explore this, this shows test-related distress as a function of gray versus orange, which is high risk for

Alzheimer's. Again, there's a statistically significant difference, but you know, we're seeing that both groups are kind of well below the line that indicates what the level of distress would be.

Again, just a similar slide showing genetic risk correlations with our behavioral measures; again, just not a lot of impact or correlation with genetic risk.

So another question that we wanted to speak to was to what extent people were sharing these test results with a healthcare provider, and then also to what extent actually sharing the results was associated with any of our outcomes. And so we were surprised, actually, that only about 10 percent of our participants went ahead and got genetic counseling from one of the Navigenics counselors, and we found that the sharing was not associated, in fact, with any of our outcomes.

On the other hand, over a quarter of our sample shared their results with their own personal physician, which we were surprised by and we found that, in fact, the sharing of results with a physician actually was associated with a couple of our -- statistically associated with a couple of our outcomes, fat intake and exercise, with the people who are sharing -- showing greater positive changes in these areas. However, we sort of see this as a finding that probably needs kind of further follow-up given that, you know, the group that shared were sort of selected, were healthier to begin with and so forth.

So we also asked about a couple of other areas, things related to self-image and other changes, and for the most part, what you can see is each of the areas we asked about -- this was a multiple-option response question -- most people said none. But we did see a small percentage of people say the way I think of myself has changed as a result of undergoing testing. A very small percentage, 10 percent, said body image has changed. So those were some additional findings from our study.

We also asked about perceptions of health. But for the most part, people said, no, my perception of my health hasn't changed from before I underwent testing.

So just to summarize. We found no measurable adverse psychological changes or improvements in diet or exercise, or increases in actual health screening behaviors. Based on our data and what people put in the intended to do, it's possible that health screening may increase in the future and we hope to be able to address this with our follow-up data. And certainly it's debatable as to whether or not this would be positive, given the limitations of the test and the cost of the screening tests.

And a large proportion of the sample that shared with a physician certainly highlights kind of the path that people are taking with this information and potentially the need for sort of taking measures to inform physicians about these tests, as we've discussed further earlier today.

But I also want to stress, there are a number of limitations to

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our study. This is a sample of convenience. We had a 56-percent response rate, so we don't really know, you know, what the remaining individuals -- how they responded. This is also based on a single follow-up assessment; also important, further based on brief measures and sort of limited to the domains that I described. And then also, of course, the characteristics of our sample are certainly not characteristic of the general population.

And I would also just highlight some future directions. I think, you know, there are many kind of remaining questions to be answered. Our study was just kind of taking a broad look at kind of what's really the overall impact in a very large group of people. But I think we've collected some data on what people are saying about sort of the salience of the diseases for which risk is provided, and I think, you know, that will be an important area to explore.

Certainly beliefs about the actionability of diseases, if people don't think they can do anything about it, why would they, you know, make any sort of behavioral changes? Certainly a level of understanding of results, although Colleen presented some nice data to speak to that issue, and also other disease risk factors and the interplay with family history and so forth.

And I'll just close by acknowledging my collaborators and funding.

DR. WATERSON: Okay, questions? We'll start right here.

DR. NETTO: Thank you. George Netto.

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An excellent study and excellent presentation. The follow-up limitation which you stated, I mean, three months follow-up, I was struck by how short is the follow-up for a study like this, and both from the negative findings point of view and the positive findings, negative on anxiety, three months, whether that's long enough, but more importantly the positive findings. Just to say they're intending to do more survey down the road, it's so easy to say immediately when you realize you're at a slightly high risk, but do they really -- I think that's a very important part.

DR. BLOSS: Absolutely.

DR. NETTO: Sorry.

DR. BLOSS: No, I would just say that I agree. And it's very hard to change behavior. As a behavioral scientist and clinician, I know that this is true. But I would also say that kind of the literature on how people respond to testing for single genes and single conditions, our findings are fairly consistent in terms of the anxiety piece, just kind of just a lack of impact. And in particular, the further out you go from testing, even the greater lack of impact.

DR. NETTO: And how was a particular test picked? Why was Navigenics --

DR. BLOSS: Pardon?

DR. NETTO: What were the criteria for picking Navigenics, for example, for this particular test?

DR. BLOSS: Um-hum. So kind of the discussions for the study, again, were going on around mid-2008, and Eric Topol, who is the director of our institute, sort of led those discussions, and I know he approached, I think, all of the main companies, deCODE, Navigenics, 23andMe, about doing the study, and Navigenics was just sort of the most amenable to kind of evaluating their test.

DR. D'AGOSTINO: I congratulate you for the presentation. I also congratulate you for the *New England Journal of Medicine* article there. Quite often when studies have such limitations, they get buried in the discussion. Yours is right out front in the conclusion.

But the question I have for you is, what can we make of the study, I mean, to inform us here? Is it that you can in fact do this testing? You can quantify these different risks, and people can respond to it. But it's such a unique population. Even the unique population itself is only 56 percent of the people that were there. You only got a 56-percent response. So I'm not clear, outside of sort of a proof of principle, in terms of how to perform these. Do we carry anything more from this? What do you think we can carry away from this?

DR. BLOSS: Um-hum. That's a good question, particularly, as you said, in light of the limitations. I think, you know, given sort of the expense of these tests, you know, and I don't know to what extent that may change over the short term, you know, necessarily, the population of

consumers that are going to be undergoing testing may really change all that much. So, you know, I think I might go so far as to say that the lack of anxiety finding, you know, may be able to serve and inform your deliberations here.

But of course, yeah, it is to the extent that as the companies, I'm sure, would like to extend their market and have consumers that aren't necessarily reflected by the demographic characteristics that I've shown, you know, it's possible that we would see different results had those people been included in the study.

But I would also just kind of sort of reiterate again that our findings in terms of harm, or at least in terms of anxiety, are very consistent with previous studies that have looked at kind of group effects of genetic testing for single genes and single conditions. So hopefully that answers your question.

DR. WATERSON: Any more questions? Dr. Moridani.

DR. MORIDANI: Thank you. I have a question for multiplex and whole genome association study interpretation results. Generally they are very large reports. Has anybody studied physicians' reactions to review of those type of interpretations? Because physicians are generally interested in three, four lines interpretation results.

DR. BLOSS: Um-hum. So you're asking, has there been studies looking at kind of physicians' response to have these tests --

DR. MORIDANI: Yes.

DR. BLOSS: -- brought to them? To my knowledge, there hasn't been. I know of some ongoing efforts in that regard. I believe that NHGRI and Dr. McBride's branch, there's a study ongoing to try to look at that issue. But, you know, again, it gets at kind of the lack of data speaking to this question.

DR. SHAMBUREK: One very short comment. Bob Shamburek.

I think another way of looking at the data is actually 75 percent of the patients chose not to give their physicians the information, which potentially could affect their healthcare. So that could've been your population, but I also think perhaps that 25 were actionable ones, but I think also that's a important potential conclusion or finding of your study.

DR. BLOSS: Um-hum, that's a good point.

DR. WATERSON: Thank you very much.

DR. BLOSS: Thanks.

DR. WATERSON: Right now we'll take a break for lunch. I'd just like to remind the Panel members not to discuss the meeting topic during lunch amongst yourselves or with any members of the audience, and we will reconvene at 1:15.

Please take your personal belongings you may want with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you.

(Whereupon, at 12:20 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:17 p.m.)

DR. WATERSON: We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relative to the meeting agenda.

Mr. Swink will now read the Open Public Hearing disclosure process statement.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this information may include a company's or a group's payment of your travel, lodging, or expenses in conjunction with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such a financial relationship. If you choose not to address this issue of financial relationships at the beginning of your

statement, it will not preclude you from speaking.

I will now go over the process to ensure a smooth transition from one speaker to the next.

So each speaker has been given 10 minutes to present. When you begin to speak, the green light at the podium will appear. A yellow light will appear when you have one minute remaining, and at the end of 10 minutes, a red light will appear and the microphone will go off. Since we have a number of speakers today, it is very important to adhere to the 10-minute time limit.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the Open Public Hearing. If recognized by the Chair, please approach the podium to answer questions.

I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair. Thank you.

DR. WATERSON: The first speaker will be Jeff Gulcher. Please come forward to the microphone.

DR. GULCHER: Thank you. Should individuals be able to directly access their genetic information without physician involvement? There are key issues when it comes to direct-to-consumer genetics, but there are traditional requirements of any genetic test, and that's no different than for direct-to-consumer genetic tests.

Analytical validation and clinical validation are very, very important, and we welcome the FDA's involvement in defining and clearing tests along those lines.

When it comes to analytical validation, there are platforms that we use where we can measure hundreds of thousands of common variants. And the accuracy of the genotyping is very, very good, 99.99 percent based on inheritance checks of large numbers of at least Icelanders who have been genotyped with these arrays, but we also further validate with bidirectional sequencing for the variants that we annotate in our profiles.

When it comes to clinical validation, in the field of human genetics for common diseases, we're blessed with very large datasets, large samples of well-phenotyped patients who have been -- whose DNA samples have been stored for years or decades, and that has allowed consistent replication across tens of thousands of patients and controls. These are much larger datasets that are typically used for FDA approval of biomarker sets. But we have that luxury because the DNA is stable and we have larger datasets.

We also bring these markers together in a standard log-additive or multiplicative model that can be validated with large datasets, and we and others have been doing so.

When it comes to the reproducibility across different companies, at clinically significant levels of relative risk, you know, twofold,

threefold, or even above 1.5-fold, there is great consistency across several of the companies. The GAO study and Venter study looked at really a relatively small number of individuals. They also looked at risk greater than one versus less than one. And, of course, when you're in these clinically insignificant levels, there will be differences among platforms based on the number of markers that are annotated for that particular test.

But that's no different than the problems that have plagued other genetic tests like cystic fibrosis or Mendelian tests. The initial panels screen only 6 out of 1,000 rare variants for cystic fibrosis and the current updated panel is about 25. So if a patient has full sequencing done by Quest, his results may be very different than the results that he gets from just screening 25 mutations. But this will be improved as we get into clinical genomic sequencing.

There are unique issues when it comes to direct-to-consumer testing. We need to be able to communicate the results in layman terms. We need to emphasize that these tests are risk tests. They are not genetic determinative tests or diagnostic tests like Nancy described with the Huntington's disease gene test.

We also emphasize that this measures just genetic risk. It does not measure the impact of family history, by and large, because the common variants are independent of family history. In fact, family history is not a very good surrogate for total genetic risk for common diseases, right? So, of

course, we expect some additional knowledge to come from beyond family history.

We also emphasize in our reports that it's important to consider other risk factors, conventional risk factors, with your physician. We also try to facilitate that by communicating results to the patient's physician, if they chose to do so, in physician-friendly terms. And I would contend that physicians these days do understand the concept of relative risk. They don't need to go back to medical school to learn Mendelian genetics.

We're talking about relative risks now. We're not talking about carrier versus non-carrier state. We're not talking about plotting risk through a pedigree. We're talking about relative risk, and they are very familiar with that concept when it comes to biomarkers, and they appear to be able to grasp that, along with the patients, as you saw today in some of the DTC outcome studies.

There is great transparency of what is measured. There is no black box algorithm that we use to bring these markers together, and we describe exactly which markers under standard RS numbers that we measure.

But there is informational risk, no question about it, when it comes to direct-to-consumer genetic tests. But there's informational risk based on any test, whether it's prescribed or whether or not a patient gets that information from a website. But a patient cannot act on this information, cannot undergo an invasive procedure, like radical

mastectomies, without interacting with a healthcare system.

So that argument, I think, is a straw man because patients need to take their risk profile and work with a physician to get a drug or to get a biopsy or an invasive procedure. So by definition, they are working with the physicians or healthcare system.

There is this possible theoretical risk that patients may, on their own, change their dose of a medication and based on a pharmacogenomic test result. And we don't offer pharmacogenomic results in the absence of a physician, only through the physician prescription.

But when it comes to the flip side, what about a patient who's considered -- is told that they have relatively or significantly lower risk for breast cancer or prostate cancer? Are they going to be less compliant for mammography or prostate cancer screening?

But I would contend that that issue is an issue that goes beyond direct-to-consumer genetic testing. That applies to any information that patients find on their own at websites, including patient risk scales. Like, for example, the American Heart Association allows one to define your own Framingham risk score. The National Cancer Institute allows a woman to define her five-year and lifetime risk. Doesn't that same informational risk apply to these sites? And nobody is suggesting that these sites should only be available to patients through their physician. So it's the same argument, I think.

You've seen some evidence today, and you'll see some additional evidence from David Kaufman later, that outcome studies looking at thousands, we're not talking about hundreds, thousands of patients who received DTC profiles for a variety of different diseases, there's really not a shred of evidence that there are harms, psychological or bodily harms or overutilization health resources so far.

So what is the risk? If we take patients who have our prostate cancer profile, for example, we include 25 common variants that have been replicated in tens of thousands of patients and tens of thousands of controls. And these are case control studies, these are prospective studies, retrospective studies.

If you take those profiles, the upper five percent of genetic risk confers an average risk of about threefold. The upper 15 percent, about twofold. The lower 35 percent, about .5-fold risk for prostate cancer. And this is independent of whether or not they have a family history.

You've asked questions about what is the validity? Does these profiles replicate in independent cohorts? Combining the markers here, this figure shows how, when we look at the 25 markers in a multiplicative model, standard model, we apply that to the discovery population in Iceland, where we discovered most of these markers, the agreement between predicted risk and observed risk when looked at from a decile point of view agrees very, very well.

And then if you take that same profile, which is just a standard log-additive model, but you could say we've defined that in our discovery population, now you apply that to a completely independent set of cohorts in Europe and the United States, you can see there's a very strong correlation between the predicted and the observed risk. For example, in the upper 10 percentile of risk, the prediction is about 2.4, and the observed risk in that decile is about 2.2.

What do we know about prostate cancer risk today? Less than five percent of men have the only risk factor for prostate cancer beyond ethnicity, and that is family history of early prostate cancer in the father. But if you add this additional genetic profile, there's another 15 percent of men who are considered of having risk that's comparable to having a family history or even greater than having a family history of prostate cancer.

These tests also seem to perform better compared to conventional risk markers, like is exemplified by this study in the *New England Journal*, where they looked at three prospective cohorts and a retrospective cohort, took 10 of our 12 markers, and the marker profile by itself outperformed the Gail score, even based on AUC. And when the markers were added on top of Gail, it reclassified another nine percent of women as having high risk, defined as the upper quintile of risk.

And here's an example of a real-life case, which is my own, which Francis Collins wrote about in his book on personalized medicine. But I

use it as an example to show that each step along the way, when I first got my deCODEme results, it showed me about twofold risk for prostate cancer, which, by the way, suggested that I have a better than even odds of not developing prostate cancer, right, just the twofold risk.

But I went to seek out my primary care physician, who ordered a PSA at a younger age than typically is recommended by most guidelines. My PSA was borderline. He recommended a follow-up with a urologist. He repeated the PSA and then performed a biopsy, and 3 out of 12 cores were positive for intermediate grade prostate cancer. But it was bilateral, which puts me at a higher risk for spread, so he recommended surgery, and then that later upgraded it to a high grade prostate cancer, Gleason 7.

But it's very important to realize that I would not have even been able to get a PSA test on my own. I would have to interact with a healthcare system. I couldn't get a biopsy on my own. I could not get treatment on my own without interacting with a healthcare system.

So it's very important to realize this information, yes, some of it can be very meaningful clinically, but patients have to seek out the help of physicians. And that's what we want them to do. We want patients to take personal responsibility.

And if one is going to use a risk-based approach to control access or regulate these diseases, it's very important to balance the harm due to delaying the new test versus to make sure that doesn't outweigh the

benefit of the additional regulation. Thank you.

DR. WATERSON: Thank you very much. We'll take questions at the end.

The next speaker is Ashley Gould.

UNIDENTIFIED SPEAKER: Just one moment. It appears we don't have her slides.

(Pause.)

MS. GOULD: My apologies for the delay. Today I'm going to cover 23andMe's position on policy and regulation, including our request for this Panel's consideration. Tomorrow you'll hear from my colleague Rose Romeo, 23andMe's senior director of regulatory affairs and quality assurance. Rose will provide more detailed and technical information related to our request.

23andMe has been proactively collaborating with the FDA, and we believe we have a clear path to pursue and obtain FDA approval of our entire genetic testing platform, though that process will take time, and today's conversation and this Panel's findings will serve to inform our path as we move forward.

Today I'll be sharing our views on the following topics. The basis of what every genetic testing service provides is information. It is critical that the information be as accurate and reliable as possible. The information must also be presented in a manner that is clear and transparent

so that it is easy for everyone, physicians, patients, and people, to understand not only what the information can tell them but also what it can't.

We already established comprehensive performance standards, and we continually work towards improving them. We also believe that our choice in partners is critical in establishing and maintaining high-quality standards, which is why we have continued to utilize the Illumina technology, which we find best in class, and also why we have a strong partnership with the National Genetics Institute, a CLIA-certified laboratory where clinical genetic testing is frequently and routinely done, to conduct all of our testing. We believe that the regulatory framework for all genetic testing companies should start with clear and robust analytical performance standards.

It's also important to look at the evolving state of clinical validity for genetic testing applications. Full genome sequencing is already here. As the technology becomes more affordable and more accessible, it's only a matter of time before we start to see the impact of full sequencing on the clinical validity of genetic tests.

For example, today clinical validity for Mendelian disorders is fairly well established, and result panels are typically based on a specific and known set of genetic mutations related to each disorder. However, full sequencing will impact results for these disorders dramatically, as we are able to report on potentially thousands of mutations related to each condition, and the specific mutations are likely to vary widely from person to person.

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Full sequencing is expected to have similar impacts to the clinical validity of pharmacogenetics and disease risk reports as well. As a result, we need to rethink how clinical validity is defined for all genetic testing.

23andMe would like to propose that a collaborative cross-sector working group be convened to clearly define clinical validity specific to genetic testing. The final definition should reflect the consensus of all relevant government agencies, multiple professional healthcare associations, such as the American Medical Association, American Academy of Family Physicians, and National Association of Nurse Practitioners and Women's Health, among others, academic researchers and representatives from private industry.

The future of genetics is clear. The widespread adoption of full sequencing is not long off. 23andMe believes that consumers and healthcare professionals have a right to access the information the latest technology can provide, as long as they are clear about the limitations of that information. As we contemplate regulatory frameworks for genetic services, it is important to put regulations in place based on the implications of evolving technologies, a constantly growing knowledge base about human genetics and the functional realities of genetic testing.

23andMe is currently an industry leader in some of today's best practices for transparency and clear communication. The following are a few examples from our service.

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We provide direct access to our white papers that serve as the basis for the reports we provide to our customers. These include criteria for including genetic associations in our reports and our consideration and methodology for how disease risk is calculated, among others.

We are confident in the reports we provide, but it is important that customers can refer directly to source information. In this regard, we provide links to published research on associations, and we continually update this information as new research is published.

We are also clear about what we test for and what we don't test for. The use of definitions and disclaimers is particularly important.

The use of graphics and charts in our various reports to visually represent data is an important part of our efforts to ensure information is communicated clearly. We believe these tools can be equally useful in a clinical setting.

Repetition is also an important element of effective communication, which is why we explicitly remind our customers in multiple locations across our website that they should discuss the results with their doctor or other healthcare professionals if they have questions about how the results may impact their healthcare.

We believe physicians and other healthcare professionals have an important role to play in direct access genetic testing and are committed to working with organizations to maximize the provider-patient relationship

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related to genetic testing.

In this regard, we think that the practical implementation of personalized medicine requires an evaluation of the current payer systems and business models for improvements to ensure that access to and use of genetic information is not burdensome on healthcare professionals, our larger healthcare system, or consumers.

We are also interested in collaborative development of CME and other professional education programs for genetic testing, together with medical schools and organizations, as discussed previously, so that healthcare professionals are prepared to incorporate genetics into their practice.

Finally, we consider ourselves industry leaders with regard to transparency and believe our experience can help inform the development of regulation. That said, there is always room for improvement. There's an opportunity to better educate people about genetics generally and our customers specifically. In this regard, we would like to work with organizations to maximize comprehension through accessible language. As the industry continues to grow, we may also need to consider providing information in multiple languages.

Ultimately policy and regulation is meant to protect people, whether you call them patients or consumers. We firmly believe individuals have a fundamental right to access directly information about their own DNA. Empowering people to become informed healthcare consumers is critically

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important to making the widespread practice of personalized medicine a reality. We also believe that whenever anyone, physician or an individual person, accesses genetic information, they have a right to genetic data that is accurate and reliable.

Protecting the fundamental right of an individual to access his or her genetic information requires adjusting some of the more common concerns about direct access testing.

23andMe has more than three years of customer insight and anecdotal evidence to draw upon. In fact, we now have over 75,000 genotyped customers, and to date we have no anecdotal evidence to suggest that any of the voiced concerns pose real, demonstrable risk to individuals.

In addition, independent studies that you've heard about today indicate that there is not this basis for these concerns. We partnered with the Genetics and Public Policy Center in their study that was not discussed today and are currently teaming up with Robert Green and Scott Roberts on a new study of reactions to personal genomic information.

It is imperative that policy and regulation be based on facts and evidence about how consumers respond to learning directly about their genetic information, rather than assumptions about possible irrational consumer behavior and fears that have not been substantiated.

Based on our experience, so much of the conversation is focused on perceived risks and concerns, so we feel it's important to take a

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moment to recognize all of the ways that direct access testing benefits both individuals and the broader field of healthcare.

The benefits serve as a foundation to preventive care, which can increase early detection rates, which you just heard about from Dr. Gulcher, which can be key to effective treatment. It is also important to recognize that people interact with their genetic information in a variety of ways, and many of these are unrelated to medical decision making.

It is only with direct access testing that individuals have greater access to participate in medical research, as barriers such as time and geography can be removed. Surveys can be completed at a participant's convenience, and a need for physical visits can be eliminated or reduced. Large numbers of participants are critical to advancing our understanding of the human genome.

Our experience shows that when individuals learn about their own data, participating in research becomes more personal and more interesting to them. 23andMe has rates of research participation which far exceed industry standards. Of our more than 75,000 genotyped customers, 78 percent have consented to participate in our IRB-approved research, and more than 83 percent of those have answered at least one survey. Our research communities also connect individuals to others with similar conditions and symptoms, providing a sense of community and support.

Direct access testing itself enables individuals to learn about

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the basics of genetics through the lens of their own data. 23andMe also provides an engaging and widely available platform for education about genetics.

We started our efforts by focusing on consumers. We have a series of educational videos and have over a half a million views on YouTube.

The policy that guides regulation must be flexible enough to keep pace with innovation and rapid technology advancement and also accommodate the practical realities and the evolving understanding of the genome. On that basis we support regulation that defines high-quality standards of analytical and clinical validity, analytical standards, and transparency.

In conclusion, I leave you with our request for your consideration. First, continue to allow informed consumers to freely learn about their own DNA; adopt thoughtful policy that promotes innovation and is flexible enough to evolve with new technologies and research developments; through a cross-sector working group, effectively define clinical validity; and, finally, focus on establishing requirements for analytical and clinical validity, analytical standards, and transparency that apply to all genetic testing services. Genetic information provided directly to consumers should be held to the same standards as information provided in a clinical setting.

Thank you.

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DR. WATERSON: Thank you. Our next speaker will be Lewis Bender.

MR. BENDER: Thank you very much. Good afternoon. My name is Lew Bender. I'm the CEO of Interleukin Genetics, a company based in Waltham, Massachusetts. I want to thank the Panel for your time in tackling this issue, and I want to especially thank the FDA for giving us a chance to provide commentary today.

I'm going to discuss the following points. I'm going to talk about our approach to direct to consumer. We're not a genome scanning company. We do single conditions at a time. I'll describe our understanding as to risk and the elements that comprise risk, regardless of the sales channel for genetic testing. Then I'll provide a framework on how one could classify risk for genetic testing, with examples, and then finally I'll describe a proposal for your consideration as to how a regulatory approach for direct access by consumers to genetic testing can be done.

Our company started in 1987. The chief scientific officer today was one of the original founders. We are a small company. We are a publicly traded company. We have a CLIA-certified laboratory, and we only sell genetic tests. We partner with companies that may have ancillary products, but we gain no revenue from the sale of these ancillary services. We only sell genetic tests.

We have a business in three different sectors. First, we try to

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provide lifestyle guidance for prevention, and we have four tests under the Inherent Health brand. We provide information for physicians, in the case here, dentists, for risk assessment. And then we've recently conducted a validation study in osteoarthritis that would allow pharmaceutical companies to identify responders and could create companion diagnostics. But I'm going to talk about the consumer side and our development efforts.

We have a very established and a very academically sophisticated scientific advisory board led by Sir Gordon Duff -- he is the chair of the Commission on Human Medicines; with Peter Libby at Harvard Medical School; Jose Ordovas on nutrigenomics -- he's the director of the nutrition genomics lab at Tufts; James Meigs, Associate Professor of Medicine at Harvard Medical School; and John Foreyt.

We interact regularly with this scientific advisory board, and we try to conduct validation studies for the genetic tests. We recently conducted one with Christopher Gardner at Stanford on our weight management test. We work with Steve Abramson on the OA project and with Joanne Jordon as well. So we try to do everything from very scientific testing with our own sponsored clinical studies.

We believe that empowering the individual to maintain good health is extremely important. Prevention, we believe, is the key to treating and improving health in the United States and lowering healthcare costs. Genetic information has the potential to personalize medicine, but also to

personalize prevention.

And genetic test information should be, to have value for the consumer or for anybody, have four properties: it should be credible, and we've talked about analytical and clinical validity; it should be beneficial, meaning you're better off with the information than without it; it should be understandable -- in a consumer setting, let me tell you, this is a challenge, but we've continuously worked with market research on the consumer to make sure they understand the outcomes, not only the outcomes but the consenting and all of the things that go into the test purchase; and there should be an actionable decision that's able to be made by the person who purchases or gets this information.

It's these actions that can lead to better prevention. We all know you should do improved diet and exercise, but how to diet and how to exercise to maintain a healthy lifestyle are important information, we believe.

I'm going to define a test as a single condition intended use. So if you're getting a scan and you're getting 500 different uses, you're getting 500 tests under the way we think, and we believe that analytical and validical quality for every single test is necessary for effective communication. We believe there should be oversight in this area.

Let me talk about the elements of risk. A test risk stems from its intended use and the consequences of the actions resulting from that information. You can mitigate the risk or you can exacerbate the risk by the

quality of that information or the way it is communicated to the end user. And we believe you can categorize test risk as high, moderate, and low, and let me go into how we would do that.

We would categorize a high-risk test as one that there could be immediate harm to the individual, and the information should only be provided by somebody who has access to the medical information in that person, of that person, a personal physician or somebody with access to a complete history, because the genetic information in and of itself is insufficient for a proper set of actions.

Certain pharmacogenomic tests should, we believe, be ordered only by the physician, because they could cause harm and they are designed to help treat -- to dose medication, which is the function of a physician, the personal physician.

We can define a moderate-risk test, which is unlikely to cause immediate harm for the user, as not necessary that the person have -- who's providing the information have the complete information package of that user. Such tests, such as risk prognostic tests, could be permitted OTC and we believe, under certain conditions, those tests could be permitted OTC, provided that a healthcare provider deliver the information, due to the nature generally in untreatable conditions or unpreventable conditions.

For treatable and preventable conditions, we really want as a broad a distribution and access for this information, because if you can

prevent that disease or extend that disease, that information could be very valuable, especially if those people can take very simple actions to direct those consequences.

A test with low risk would be one, due to the nature of the intended use, with that information is really very unlikely to cause harm, even if it's misunderstood, even if it's a false positive or a false negative. Delivery of that information is not necessarily needed by a trained individual, provided you have a credible test, beneficial, understandable, and actionable. We believe certain nutrigenomic tests should be permitted to be sold DTC, and these would be examples of a low-risk test.

We believe that there is a regulatory strategy for all genetic tests, and for any level of risk, we expect that there be adequate scientific support for the validity of that test, that there be a laboratory that is qualified, and we don't believe that it is necessary to recreate the CLIA regulations in another agency. We believe CLIA is an adequate certification process for the genetic tests. And we believe proper information prior to the taking of that test, proper consent, understandable information, and a full set of disclosures is necessary for adequate protection to the consumers, and we support the UK commission recommendations in this area.

We would propose that, for moderate-risk and low-risk tests -- we do not believe high-risk tests should be allowed to be sold direct to consumer -- that meet the medical device standard under 21 U.S.C.

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Section 321(h), that companies should register these tests and list these tests with FDA and that the companies should list their CLIA lab certificate number and whether the test is low or moderate risk and what the intended use is.

We do not believe pre-market submission is necessary.

However, all tests for moderate risk should include a disclaimer that the test has not been reviewed by FDA.

Increasing access to quality information can be provided by genetics and allow individuals to take greater control of their health and their wellness, and maintaining good health is very important. Direct-to-consumer testing and genetics in general offer great potential benefit. Precautions and standards, as we've just described, are needed for the public as well as for the consumer. Thoughtful consideration, which we appreciate is being done here, is necessary to assure that the private sector's innovation continues to progress and translate genetic science into available and useful products and services.

So we put forth in our letter that's, I think, in your docket, dated March 1st, some of our details in more greater -- more greater detail in that letter.

We believe that the market forces will ultimately eliminate genetic tests that are not of value, as we've seen in Dr. Mansfield's presentation. However, given the importance of this field, we do believe that oversight, as we've outlined, is needed to assure that those services that do

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reach the market are not harmful, are not false, are not misleading, and do not damage genetic science or the companies that are trying to create validated, high-quality science in areas for which unscrupulous people have been known to work.

Once again, I thank you for the opportunity to speak, and I'll answer any questions at your convenience. Thank you.

DR. WATERSON: Thank you very much. The next speaker is Jeremy Gruber.

MR. GRUBER: My name is Jeremy Gruber. I'm the President of the Council for Responsible Genetics. CRG is a public policy organization that represents the public interest and fosters public debate about the social, ethical, and environmental implications of genetic technologies. I think so far I'm the only person without a financial interest in this conversation. We appreciate the opportunity to comment on direct-to-consumer genetic testing, our concerns regarding consumer protection, and the need for responsible regulation.

The Human Genomic Project is properly regarded as one of the great scientific achievements of this generation. Since then, new technologies have emerged that are equally significant: reducing the cost of whole genome sequencing to a small fraction of the original cost and continuing to make impressive strides towards introducing genomics to the broader public through clinical applications of this technology.

As the science progresses, it has become clear that the major challenge for the future won't be sequencing technologies and broad public access to them, but rather the cost and difficulty of interpreting and applying the huge amounts of data that they generate. We are still only at the beginning of this genetic revolution, and it's certainly our hope that this new synthesis of genetics and information technology can empower individual self-knowledge and promote health access across a wide variety of platforms. Yet, how medical care will be ultimately personalized is still quite unclear.

As physicians move slowly to embrace genetic testing prior to the robust development of scientific knowledge and understanding over the relationships between genes, human health, and the environment, private firms have scrambled to fill this void by offering these testing services direct to consumer. These companies offer individuals the opportunity to discover if their genomes possess SNPs and in some cases known Mendelian variants associated with disease and cancer risk, nutrient metabolism, drug response and metabolism, and recessive carrier states, among others.

They further offer risk assessment services which look at several genes simultaneously to give probabilities of disease development over one's lifetime and offer diet and lifestyle recommendations on the basis of these genetic test results.

It's difficult to speak about the current state of the industry as a whole, since there are some companies, such as 23 and Navigenics, that use

high-quality genetic testing and who seek to leverage published and peer-reviewed scientific evidence, and many other DTC companies, such as a few that have been already discussed, that are essentially fraudulent in their laboratory testing or claims. However, there are significant concerns that we have for the industry as a whole, as it currently operates without regulation.

Let me be clear. The call for regulation of DTC genetic testing is not some paternalistic denial of individual access to one's own genome nor some blind adherence to medical tradition. We believe everyone should have access to their genome and be able to sequence it if they choose. What we do feel strongly about, however, is that people shouldn't be misled about the significance of that information and that people should be able to be assured that the claims that are made are accurate and that their privacy will be protected. We must acknowledge that information could cause both direct and indirect harm as well as good.

The value of DTC genetic testing to most consumers, the reason why most consumers would pay these private companies to sequence their genome, is not for the sequencing itself but for the perceived benefit of learning what sequencing means for their health and that of their family.

Science itself is incremental, and what we've learned through example after example over decades is that when dealing directly with human health, the integration of science with medicine and other consumer applications must be careful and methodical. The marketing of genetic tests

to consumers is following a path similar to direct-to-consumer marketing of prescription drugs. But unlike prescription drugs, genetic tests do not have to be federally approved or validated, and some of these tests may or may not do what the companies claim that they do.

Furthermore, genetic tests are often patented. There are rarely second opinions or the possibility of retests by another company. Consumers have no recourse.

Reputable DTC companies may very well be doing a decent job of reliably telling the consumer which nucleotide they have at a given position. These companies are in a difficult position, however. They attempt to market their services, while at the same time communicating the current limitations of what we can learn from genetic information. This may be one of the reasons they regularly caution that what they are offering isn't medical advice.

Yet it is easy to overstate the significance of genetic tests results, particularly those tests for which reliability has not been certified and standardization has not been set by a professional genetics association.

And these companies want to have it both ways. They know full well that few consumers will purchase their products unless they can directly see the benefits of that information. And so these companies regularly make and market suggestive statements to the public.

23andMe's website states, "Take charge of your health and

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wellness. Let your DNA help you plan for the important things in life."

Navigenics' website offers "A new look for a healthier future." deCODE

Genetics promises to "deCODE your health." And Pathway Genomics claims

that "It's now possible to know how genes may affect your health."

Every player in the industry makes both explicit and implicit claims that knowing your genetic information will demonstrably improve your health. With a few exceptions, science is still progressing towards being able to make that claim.

As the recent investigation of the DTC industry by the GAO office clearly demonstrated, there's just no way of reconciling industry claims that the information they are providing is ready for provision directly to the consumer with the fact that reputable companies conduct analysis on the same DNA and come up with radically different interpretations.

Indeed, as research develops, we are learning that genetics is only one small part of our risk for most of the diseases and conditions that these companies test for because the causation of these maladies is multifactorial. The reason offered as to why DTC companies come up with different results is simply that different companies are testing a different set of variants.

The solution they offer then is that an agreed-upon set of common standards would solve the problem, but this is only partially correct. The reason why this is not a complete solution is that we are still learning

how to aggregate independent risk factors into a net risk score. Genes interact with each other in the environment in ways that we are only just beginning to understand. Even if there was agreed-upon standards and all of these companies came up with the same risk prediction as a result, we just simply don't know enough at this point to know whether in most cases that prediction is a correct one.

A small percentage of the information that DTC companies offer, like BRCA 1 and 2 testing, are very predictive, as these disorders are more fully penetrant and in the right circumstances have important medical implications for a small number of people. In most cases, though, the magnitudes of the risk shift that DTC companies are giving people has limited value.

Finding out that your risks are slightly increased or decreased over the general population is essentially meaningless, since these are common diseases that we remain at significant absolute risk for whether or not we are at some relatively increased or decreased genetic risk. Moreover, this information is still delivered without reference to family history or lifestyle, which makes it even less reliable as a risk indicator.

Now, some have argued by analogy that cholesterol and blood pressure are regularly tested for and they confer only subtle, relative risks for heart disease, and this is similar to the degree of risk conferred by genetic variance, and that is true. But what they fail to mention is that your doctor

doesn't check your cholesterol because they're primarily seeking predictive information. Your doctor checks your cholesterol because they can change your cholesterol. That is the value of such testing. By contrast, offering information about something such as diabetes risk by genotyping without referenced information about family history, weight, or blood glucose is both misleading and harmful to the consumer.

The potential for harm to the consumer rises significantly when these companies combine clinically meaningful rare DNA variant information along with clinically much less relevant common DNA variant information, and further pairs such information with pure entertainment such as, for example, genetic tests for whether you have thick earwax.

We are still only beginning to learn how consumers understand and react to such information. As we've already heard today, some preliminary studies have had severe limitations in terms of representative populations. As the industry grows to serve larger and larger proportions of the general public, it is the duty of the FDA to ensure that the public is protected.

CRG strongly believes DTC testing should be regulated and recommends that the following steps be undertaken. Some, but not all, DTC companies voluntarily engage in some of these practices to varying degrees. We believe they should be mandatory.

We must insist on the provision of accurate and transparent

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information to consumers. We must not only require the CLIA-certified laboratories be used but also acknowledge the limitations of CLIA certification and require more rigorous standards for analytic validity. Specifically, DTC firms should disclose, as part of pre-market review, data demonstrating a high level of analytical validity for all tests.

DTC firms make broad claims about the association of certain SNPs and real human phenotypes, ranging from single-gene diseases, such as cystic fibrosis, to far more complicated and poorly understood multifactor diseases such as diabetes. While some of the associations are grounded in rigorous scientific literature, many may not be. We believe the pre-market disclosure of the relevant research demonstrating the validity of health claims on the basis of genotyping should be required. This should include the sensitivity, specificity, and predictive value of the test, as well as the populations for which it has been studied.

DTC firms also interpret genetic test results to give estimated numerical probabilities of disease risk rather than narrower claims of positive or negative association. CRG encourages FDA to require DTC firms to disclose evidence regarding the accuracy and scientific validity of the methodology used in making these interpretations.

Some DTC companies make health and lifestyle recommendations on the basis of genetic risks they find. An analysis of these recommendations for scientific validity and clinical efficacy should also be

disclosed.

Adequate genetic counseling should be provided to assist consumers and patients in interpreting and acting on their genetic test results, and DTC firms must clearly and understandably disclose any risks associated with making decisions on the basis of genetic test results.

Finally, we have a number of concerns regarding DTC genetic tests that are not being addressed by these hearings. We are concerned that after a year of federal regulatory review of the DTC industry, that the FTC has not taken a visible role in such review. We urge the FDA to bring the FTC into this process to ensure that the consumer is protected from inaccurate and untruthful marketing.

Finally, we are concerned about the significant and unique consumer privacy issues implicated by DTC that are not being addressed by this inquiry, including ownership of genetic information, clear guidelines as to industry controls to ensure that customers are submitting only their own DNA, so-called surreptitious testing, to security safeguards for such data and disclosure of customer data to third parties without sufficient consent. We urge the FDA and other federal agencies to open separate inquiries into these vital consumer protection issues. Thank you.

DR. WATERSON: Thank you very much. The next speaker is David Kaufman.

DR. KAUFMAN: Good afternoon. Thanks so much for allowing

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me to speak. I hope we can show you a couple of interesting data points from a survey that we did on three companies, deCODEme, Navigenics, and 23andMe's customers a few months after they received their genetic testing results.

And I'm Dave Kaufman. I'm from the Genetics and Public Policy Center at Johns Hopkins.

I guess one other thing I would say quickly is that there are a couple of comments, or at least one, about sort of irrational concerns about DTC and maybe that there's not a shred of evidence that there are any harms. I would sort of caution the other side that we shouldn't -- you know, caution you about sort of irrational exuberance about the data so far.

We all know that there are many, many companies that are interested in producing DTC genetic results and selling them to folks. We don't know exactly where this is leading us. Some people feel that it is leading us to the Land of Oz, where we will realize the benefits of personalized medicine, and others feel that there are risks and dangers that need to be considered. No matter what side you fall on, or you may fall on both sides, depending on the argument, it's definitely clear that we're no longer in Kansas anymore.

There are obviously several valid concerns about DTC testing, the validity and the utility of the tests, the fact that many of the risks and benefits aren't well understood, that the vendors may be making misleading

or unwarranted claims that lead people to purchase the tests for the wrong reasons. There's concern that consumers may be unable to interpret the data and we don't know yet what people will do with it.

And so we have joined the effort to start collecting some empirical data to help answer these questions, and I'm going to talk today about the bottom three things, why people are purchasing the data, a little bit about how they interpret it, and a little bit about what they've done with things so far.

So to measure DTC consumer perspectives, we performed an online survey of three companies' customers. Those are the prices that folks were paying during the time that we did the survey. The companies themselves contacted the respondents by e-mail. They took random samples of their customers. The survey took about 20 minutes, and it was performed last spring, winter and spring.

And we got a 37-percent response rate, and of those, 90 percent qualified to take the survey. We disqualified people who weren't from the U.S., who hadn't viewed their results, who either -- who had the test paid for by someone who worked at the company, and there were a couple of other disqualifiers, which I can't remember off the top of my head.

We were trying to sort of find out who's purchasing these tests, why are they purchasing them, what's their sort of overall reaction to the results, how well do they sort of interpret and understand some of the data,

and what are they doing with the information?

The major limitations of the survey were, first, that it was a cross-sectional survey. We talked to people at one point in time after they got results, so there was no follow-up to see how what they told us changed. We did not collect any data on people's specific genes or their risks, in order to maintain confidentiality. And we analyzed all of the data in aggregate, that is, we combined the data from all three companies. We agreed to do that in order to protect each company from having specific things said about them, and our goal wasn't to compare different methods or say that one is somehow better than the other.

I don't want to spend a lot of time on this slide, except to say that the left column shows the demographics of DTC customers. On the right is the U.S. population. And DTC customers that we talked to, on average, had higher incomes than the rest of the United States, were very highly educated, and white non-Hispanics were over-represented in the customer base.

So why did folks decide to get this testing? Forty-two percent said they were interested in at least one of the specific health conditions that the company tests for. Of those, we asked about different categories of disease, and the most important ones to people were cancer, cardiovascular disease, and neurological diseases. Response to medicine down at the bottom. I think people don't maybe know about that as much.

A third said they were interested in part because first-degree

relatives had been diagnosed with one of the medical conditions that are included in the service, which hearkens to what Jeremy was saying about the importance of including family history and the associated risks there.

And we asked people how important were the following different sorts of things when you were considering whether or not to use the company's service? Ninety-four percent said it was important to them to satisfy their curiosity, 9 in 10 wanted to know what diseases they were more likely to develop, that they were at high risk for, and 90 percent -- this excludes the Navigenics folks from the denominator because they didn't get ancestral data, but 90 percent said they did it to learn about their ancestral roots. And down at the bottom, you see that seven percent said that a doctor's recommendation was important to them. And round about the middle, 77 percent said that it was important to them to learn how to improve their health.

So what do people sort of think about the data that they were given? Across sort of the summaries or how satisfied were you with the service, 88 percent of people said they were very or somewhat satisfied, 10 percent didn't want to take a position, and only two percent said they were dissatisfied or very dissatisfied. That level of satisfaction was fairly consistent across demographic groups. You see gender in purple, race and ethnic background in green, education and income.

What were some of the sort of more detailed reactions to the

services? Eighty-nine percent said that they satisfied their curiosity with the results, eight percent said that they felt there was nothing they could do to change their health risks, and about half of the people said they had sort of gotten some relief from an uncertainty about some aspects of their health.

Thinking about the sort of clarity and value of the information they were given, 88 percent said the reports were easy to understand, 84 percent felt that the value of data was worth the cost, and 38 percent felt that the conclusions they received were too vague. And we acknowledge that that sort of question is too vague, but --

(Laughter.)

DR. KAUFMAN: -- those are the exact words we used.

Just one little cross-tab for you. This is sort of how satisfied were you by whether or not you thought the reports were easy to understand. So people who felt they didn't understand the data, far less satisfied with it.

So on to sort of how people interpreted the results. Fifty-eight percent said that they learned something that they could use to improve their health that they didn't already know. We don't know the details of that. Satisfaction did vary by that.

Then we wanted to see if people understood the data that they had gotten. So participants were shown two hypothetical test results using the exact format that the company uses in its report. So everyone who got --

that used 23andMe saw two 23andMe reports. I'm going to show you one from Navigenics and then one from 23andMe. But everyone got two things from the company they purchased from.

So in the first scenario, we told people that Mary gets a result that her estimated lifetime risk of diabetes is 25 percent compared to 30 percent in the general population. And then here's an example of what we showed 23andMe customers. For the second result, Mike has an 11 percent chance of developing colorectal cancer compared to 5 percent in the general population.

And we asked them, based on the information above, which of the answers best describes how Mary and Mike's risk of disease compares to the average person's risk? So for Mary, when the risk was lower than the population, five percent said that she was more likely to get the disease and two percent said they didn't know. We sort of felt like it's not fair to count against people who said that they have the same risk because you could easily say, well, those things do seem reasonably similar to me. So seven percent of people didn't understand the low-risk finding. Four percent misinterpreted Mike's result of high risk.

And just sort of a curious finding, that if you sort of control for everything, the difference between the seven percent and the four percent is statistically significant. So it seems that people were having a harder time interpreting risks where they're sort of under the, you know, lower risk of

disease than higher risk. And that could be a numeracy issue, it could just be sort of what people are looking for, but you know, a little bit interesting.

Looking at sort of the percent of people who got incorrect answers on these two things, Mary's diabetes in green, Mike's colorectal cancer in red, the percent that got it wrong does increase as education decreases. Although I would note that seven percent of people who are very, very educated did not get -- did not understand all the results.

And then on the right you see the breakdown by people who thought that the reports were easy to understand and people who didn't think the reports were easy to understand. The people who didn't think they were easy to understand were telling the truth about their interpretations.

So what did people do with the data? Twenty-eight percent discussed results with a healthcare professional, and within that group, 20 percent had discussed it with a primary healthcare provider, 1 percent contacted a genetic counselor, and 19 percent had talked to other healthcare professionals, and 9 percent of people had followed up with additional laboratory tests. Again, we don't have any more detail on that.

Sixteen percent said they changed medications or supplement regimens based on the data. Most of those people had changed dietary supplements, four percent changed a prescription in consultation with a doctor, and 1 in 200 people did change their prescription without consulting the doctor. It should be noted that, among the people who changed one or

more of their regimens, 54 percent had shared their information with a healthcare provider.

Were people changing their behaviors? Thirty-four percent said that they were being more careful about their diet. This is, again, at one point in time, two to eight months after they got the results. There was one person who said they were letting themselves go.

(Laughter.)

DR. KAUFMAN: And 65 percent said they were sort of carrying on as they were. Fourteen percent said that they were exercising more, 31 percent were more determined to exercise, and the rest hadn't changed. No one said they were exercising less, although it is hard to exercise less than zero, as my gym knows very well.

(Laughter.)

DR. KAUFMAN: So just sort of a conclusion. Demographics of the early DTC customers are quite different from the sort of general U.S. population that needs to be sort of taken into account. People are very curious about what might ail you. It's very highly valued. We have some other data on that that I didn't show you. Satisfaction with the results seems to be fairly high, though not among those people who found the reports difficult to interpret.

It appears that at least some of what the companies are trying to communicate to their customers is being well understood. You know, 93

to 96 percent being able to interpret the result. That's very, very different from the question of whether the information that they're being given is accurate or valid.

There are some measurable issues with the interpretation of the results, which suggests to us that there is room for improvement in the reports. And there do seem to be some behavioral changes. We don't know if these are good or bad. We don't know if people are adopting good exercise regimens, better diets, appropriate diets. We don't know if these changes are transient or lasting.

None of what we're reporting is the same as actual outcome data. It is sort of suggested that there may be some general benefit to receiving this kind of information. But it is suggestive, and longitudinal studies with richer data are needed. Of course, the classic more data is needed.

Thanks again to you all for having me and to everyone who collaborated; I appreciate it.

DR. WATERSON: Thank you very much.

DR. KAUFMAN: Thank you.

DR. WATERSON: Our last speaker this morning is -- I'm probably going to murder the name -- is Ann Maradiegue.

DR. MARADIEGUE: I have no financial relationship to disclose. And Mr. Chairman, members of the Committee, I'm Dr. Ann Maradiegue, an

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Assistant Professor at George Mason University in Fairfax, and a primary care family nurse practitioner. I am presenting on behalf of the American Nurses Association. The American Nurses Association appreciates the opportunity to testify related to regulation concerning direct-to-consumer testing.

The ANA was founded in 1896 and is the only full-service national association representing the interests of the nation's 3.1 million registered nurses, and advances the nursing profession by fostering high standards of nursing practice, promoting the rights of nurses in the workplace, and sharing a constructive and realistic view of nursing's contribution to the healthcare of our nation.

Through our 51 state and constituent member associations, the American Nurses Association represents registered nurses across the nation, in all practice and educational settings. The American Nurses Association commends the FDA Advisory Committee for their work in identifying and making recommendations related to the regulation of genetic testing.

I have practiced as a licensed family nurse practitioner for 16 years, and I screen and order for genetic tests based on my patient's needs and risk profile. I appreciate this opportunity to discuss the FDA's regulation of genetic tests and the role of the nursing profession in genetic testing.

Genetics and genomics are expected to revolutionize the future of healthcare and also the health of the public in the 21st century. The translation of genetic and genomic technologies and information into

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healthcare has unprecedented implications for the future of the public's health, and nurses are an integral part of that future.

Today there are three key issues that I want to bring to your attention. The role of nurses, including advanced practice nurses in genetic services and genetic testing; who should order genetic tests; and what the nursing profession's perspective is on the regulation of genetic tests, including direct-to-consumer genetic testing.

Nurses are the largest healthcare group, and according to the 2010 Gallup poll, they continue to be the most trusted healthcare professions in the U.S. Nurses are essential in helping patients and families navigate the new world of genetic services and testing and also fill a critical shortage in the number of healthcare providers' skill to deliver genetic services.

This year, the Institute of Medicine released a report stating that nurses should be full partners with physicians and other health professionals in redesigning healthcare in the United States. This means that nurses should be among those involved in all decisions that are related to patient care and genetic testing.

Between 10 and 20 million Americans have or will develop one of the more than the thousands of known genetic diseases throughout their lifetime. The era of genetic/genomic testing is here, and the number of genetic tests for these diseases is growing exponentially.

There are over 220,000 advanced practice nurses who are

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licensed and credentialed. They have substantial knowledge and expertise in being a primary care provider, which may include genetic services and testing. These nurses are allowed to order, bill, and are reimbursed by third party payers for genetic services. The FDA should not make rules that would inhibit or interfere with the advanced practice nurse's ability to order or be reimbursed for genetic services, including genetic testing as allowed by current laws.

Who should be able -- allowed to order genetic tests?

Providers, both physicians and nurses, who are qualified and licensed should be allowed to order genetic tests. Qualified individuals know the optimal test for a given circumstance, what laboratory and technique is appropriate for the specific genetic test, how to interpret the test results, how the test results will inform healthcare decision making.

Qualified individuals also have the skills needed to convey the test results that are unexpected or uncertain, such as variants of uncertain significance. And they also convey to their patient and family how the meaning of the results and the healthcare management may evolve over time.

Should direct-to-consumer testing be regulated? Absolutely yes. Existing regulation of genetic tests for analytic and clinical validity, as well as clinical utility, remains extremely limited. Currently, the only regulations that have an effect on genetic testing are a result of the Clinical

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Laboratory Improvement Act, CLIA. However, CLIA doesn't actually regulate testing; it certifies laboratories who perform the testing.

According to CLIA, genetic tests are considered high complexity, which indicates a high degree of knowledge and skill required to perform or interpret the test; therefore, laboratories conducting high-complexity tests must undergo proficiency testing at specified intervals. However, a specialty area specific for molecular and biological genetic tests has yet to be established by those who administer CLIA.

As you know, genetic tests fall into two primary categories: test kits and laboratory developed tests. To date, the FDA only regulates as medical device genetics tests associated with test kits. According to [genetests.org](http://genetests.org), there are more than 2,000 clinically available genetic tests. However, most are laboratory developed tests and do not fall under FDA regulations. This includes most direct-to-consumer genetic tests currently available to the public. There is no established mechanism to determine when a genetic test has sufficient analytical and clinical validity to be accurate, as well as the clinical utility to be beneficial to the consumer.

In summary, laboratory developed tests including many of those offered direct to the consumer are subject to the least amount of regulatory oversight as neither CLIA nor the FDA evaluate the laboratory's proficiency in performing the test or clinical validity relative to the accuracy of the test to predict a clinical outcome.

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It is the position of the American Nurses Association and the nursing community, a profession whose role is, in part, to assure the safety of the public, that the FDA regulates genetic tests to enhance public safety. In addition to supporting qualified nurses as appropriate providers in order to discuss genetic tests and results with the patients and families, the American Nurses Association recommends that the FDA partner with the Division of Nursing/HRSA and other federal agencies in studying the agenda for and supporting nursing education in genetics.

The FDA should assure that funds are provided for nursing education in genetics and genomics that can build on already established nursing genetics and genomic core competencies. This funding should be in addition to and not dollars taken from any other existing program for nursing.

The NIH National Institute for Nursing Research should continue its emphasis on nursing research, its Summer Genetics Institute, and should redouble their efforts to recruit nurse scientists from diverse backgrounds, including minorities. Nursing has played a leading role in the development and implementation of genetic and genomic education programs and establishing genetic/genomic professional competencies regardless of professional specialty or educational training.

In summary, I would like to reiterate that nurses have an important role in genetic services. Advanced practice nurses are well positioned to provide genetic services and order genetic tests. The FDA

should do nothing to inhibit and, in fact, should support an increase in the number of qualified advanced practice nurses. The FDA should also regulate genetic testing.

The American Nurses Association recognizes that the genetic and genomic discoveries have the potential to improve the public's health and decrease disease burden, but this can only happen with regulations that assure public well-being and safety.

Once again, the American Nurses Association thanks you for the opportunity to testify before this committee. The American Nurses Association appreciates your clear commitment to nursing and your understanding of the important role nurses play in the provision of essential healthcare services.

The American Nurses Association and nurses around the country are ready to work with policy makers, leaders in healthcare, and other providers and consumers to make the use of genetic testing and information provided to patients safe, effective, affordable, and understandable to all Americans. Thank you.

DR. WATERSON: Thank you very much.

At this time, I'd like to ask members of the Panel if they have any questions for the speakers and would the speakers please come up to the podium? Yes.

DR. DAVIS: My name is Margaret Davis, and I'm the Consumer

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Rep for this meeting.

Ms. Ashley Gould made a statement that -- about she has about three years of data and 75,000 genotyped customers. And then a question further crossed my mind, and then when Jeremy got up and made the statement about these data may be patented, the question I have is if I decided to get myself genotyped, what is the trail for the data for my personal biological data, I mean, samples? Where does it go? If I need it to use it again, could I and what does that do for -- do you use it for research, or can you use it any way you want, or does it belong to me?

MS. GOULD: So we're very clear that your data belongs to you. We have a section of our website where you can actually download your entire raw data so you can take it anywhere you want, and there are a lot of people who have done a lot of ancestry. We have a section on our website about ancestry, so there's a lot of interest in genetic genealogy, so a lot of people do that. People also use it.

There are other web applications where you can put your genetic data and get different interpretations, that sort of thing. So we absolutely -- your data is your data. We do conduct research, as I was also talking about. So we have an IRB-approved consent form that's optional, so you either opt into that or not. You can also withdraw at any time. And if you opt into that, then we can use your data in studies that we can publish on. We also can use data for internal R and D purposes, even -- under our

terms of service, but we can't use that for published research.

DR. DAVIS: Thank you.

DR. D'AGOSTINO: I have a question of the first speaker, and possibly it spills into others.

The question is in terms of the presentation, we were shown deciles and invalidation. The interpretation I heard you give was the upper 5 percent of risk or something like that. When you do these deciles and you make a presentation, are you talking about absolute risk or are you talking about risk particular to a population? Do you need calibration as you go from one population to the next population? And are these risks being computed solely on the genetic information without anything about lifestyle or anything about demographics?

DR. GULCHER: So what I showed you was just simply genetic relative risk, so we're not including family history, we're not including any other risk factors. And so we're only measuring the upper 10 percentile or the next 10 percentile when we're doing the decile plot defining what the relative risk --

DR. D'AGOSTINO: The cut points for those deciles change from population to population?

DR. GULCHER: No, it's defined by -- we give the predicted risk and we look at the observed risk within those populations, so we take the population of Iceland, as an aggregate, and then we took three other

European populations plus the U.S. population, and we simply showed you the aggregate data. So if there's any noise that is added because the difference --

DR. D'AGOSTINO: The question would be, for Iceland would be, upper risk would be 50 percent; for another population, would it be 10 percent? Your cardiovascular risk change from population to population and is -- are you saying that this is impervious to that?

DR. GULCHER: That's what I said, that this relative risk. This is not absolute risk. What you just described is more absolute risk.

DR. D'AGOSTINO: Then I'm not sure I know what you mean by these deciles of relative risk.

DR. GULCHER: It's risk of the patients within that particular decile, for example, in the other upper 10 percentile. It was predicted that they would have about a 2.4 --

DR. D'AGOSTINO: Yes, that's absolute risk. That's not relative risk.

DR. GULCHER: Well, I define it as relative risk.

DR. D'AGOSTINO: Relative risk is -- my -- 2 percent, my relative risk was 2, that means I'm twice as likely to get something than another, than the comparative group, but it doesn't tell me what the comparative group has as their risk. It just tells me I'm twice as likely.

DR. GULCHER: Right. And then we compare that prediction

with a large set of patients who develop the disease versus a set of patients who didn't develop the disease. That's the comparison.

DR. D'AGOSTINO: And that's absolute risk when you're pulling in. So the risk, the absolute risk, is common across populations?

DR. GULCHER: Yes. If you look at the genetic markers that we have and you look at cross populations, not only do these markers replicate with admittedly modest relative risk or odds ratios ranging from 1.2 to 1.8-fold for prostate cancer, but the estimates of those risks are fairly comparable population to population, whether it's the Mayo Clinic or Hopkins or several of the other sites that we had used for replication purposes. Those are the initial --

DR. D'AGOSTINO: The relative risks are --

DR. GULCHER: That's right.

DR. D'AGOSTINO: -- comparable and --

DR. GULCHER: That's right.

DR. D'AGOSTINO: -- we don't know what the absolute --

DR. GULCHER: That's right.

DR. D'AGOSTINO: And what's this moderate risk and high risk and low risk? What does that mean? I mean, high risk means 5 percent are going to die or just means --

DR. GULCHER: Yeah. No, we --

DR. D'AGOSTINO: -- that you're twice as likely --

DR. GULCHER: I did not define --

DR. D'AGOSTINO: No, no, no. You didn't. But I'm asking you and that's why I say --

DR. GULCHER: Yeah -- so what I emphasized was the risk, clinically significant risk, differs depending on which disease you're looking at. A relative risk of 2 -- or sorry, relative risk of 10 for a disease like Crohn's disease may not be as important as a relative risk of 1.5 or 1.8 for a common disease like --

DR. D'AGOSTINO: That's right. You don't --

DR. GULCHER: -- prostate cancer --

DR. D'AGOSTINO: -- have to worry about the prevalence in incidents, exactly.

DR. GULCHER: I'm sorry?

DR. D'AGOSTINO: You have to worry about the prevalence in incidents --

DR. GULCHER: Yeah, but in the calculations of relative risk, if you are -- most of the studies are done where you're looking at population-based assessments of allelic frequencies. So you don't need to know what the prevalence of that particular disease is in that population. All we're doing is defining a relative risk, and in some cases we're defining what the --

DR. D'AGOSTINO: So you're saying your relative risk may be 10 --

COURT REPORTER: Excuse me. One speaker at a time, please.

DR. WATERSON: One speaker at a time, please.

DR. D'AGOSTINO: I'm sorry. I thought he finished. He did finish.

So you're saying that, I give you a relative risk of 10, but I don't give you any indication of what your real probability --

DR. GULCHER: Yeah. No, for a disease that's not very frequent like Crohn's disease, okay, with a prevalence of .1 percent, a tenfold increase risk for Crohn's disease means that your estimated lifetime risk is only going to be about 1 percent. So information like that may not be as useful unless the patient is already symptomatic, comes with chronic diarrheal problems, and this increases the index of suspicion for Crohn's disease.

DR. D'AGOSTINO: So you turn the relative risk into an absolute risk to interpret it?

DR. GULCHER: That's right, yes.

DR. D'AGOSTINO: And that's my question. Are you doing that?

DR. GULCHER: Yes. But the plots that you asked about, the decile plots, that's just simply relative risk as defined.

DR. NETTO: Yes, my question is to the same speaker, the first speaker again. Sorry about that.

So you made the statement that there's no shred of evidence, and it was somewhat emphatic, that there is any harm with this testing. Do

you define over-treatment as a harm, potentially? And do you believe that even as it's been done on several thousand people, two, three thousand, that these studies have adequately evaluated any potential outcome harm from these tests?

DR. GULCHER: No, no. Not at all. What I emphasized was, based on the thousands of patients who have been studied, and admittedly, there are limitations to those studies, but so far there hasn't been any evidence of the harms that Nancy Wexler referred to in the context of Huntington's disease testing.

DR. NETTO: And do you agree that these, most of these studies have looked at the issue of anxiety but really have not looked at issues, did it really help the patient or not or did it really harm the patient or not?

DR. GULCHER: That's right, yeah. You would need to have long-term outcome studies on the orders of tens of thousands of patients, probably, for each major clinical indication. You have to follow them probably for 5, 10, 15 years to actually look at the balance between harms, of over-treatment or under-treatment, versus the beneficial effects of the testing.

DR. NETTO: You mentioned the prostate cancer example, which is a prime example of potential over-treatment for people who are seeking PSA, which all the problems for PSA and over-treatment that the literature is dealing with. That's why I wanted to come back to it.

So probably a more accurate statement would be there's no evidence yet that it induces anxiety in this population in the first three months or six months, but really, we don't have any evidence about the outcome and how these tests are helping us better treat or worse treat the patients.

DR. GULCHER: Well, we do have clinical utility studies that have shown that genetic information can improve the positive predictive value of a biomarker test like PSA in terms of biopsy outcomes. But in terms of long-term benefit of those outcomes, that would require, of course, a long-term study.

DR. NETTO: But evidence-based studies combining these genetic studies with PSA show superiority, right?

DR. GULCHER: Yes, yes. We have these -- yeah.

DR. MAHOWALD: This is a question that picks up on a statement that Jeremy had and a question that I raised earlier this morning, and it would be directed to any or all of the first three speakers.

Jeremy mentioned that there seems to be no way in which to ensure that the tissue or the buccal smear or whatever is used in order to do the genetic test comes from the person who's paying for it. And so I wonder if any of our first three speakers, in their own companies, have a way through which they already have addressed that issue or might address it.

MR. BENDER: This is Lew Bender from Interleukin Genetics.

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Anybody can purchase the test, so we don't know if the person who purchases it sends it in, unless we see it coming back with that name. If we get a test in that comes with a name and they've got all their information and they attest, in their certification and consent that it is them, we accept that.

And it's very challenging for us to imagine that somebody would swab someone -- you know, swab either themselves and send it in under another name or be forcibly swabbed by -- in the mouth. It takes about 30 or 40 seconds to swab on each side of the cheek, and then you have to let it dry and send it in.

So it's possible that people could be swabbing other people and sending them in, but we would think that it's very unlikely that somebody who swabs themselves, sends it in and consents and that's their signature, isn't that person. There's no way to prove that --

DR. MAHOWALD: No. No, there isn't.

MR. BENDER: -- but we would believe that if a person purchased the test and then we saw that the purchaser sent it in and they, on the consent form, attested to it, since it's kind of a procedure to do, we would expect --

DR. MAHOWALD: Is it always attested to?

MR. BENDER: Yes.

DR. MAHOWALD: I mean, is -- what about children?

MR. BENDER: We do not accept from anyone under the age of 18.

DR. MAHOWALD: Would you accept it from an adult who, in some way -- or would you accept that a person might obtain a specimen from a disabled adult?

MR. BENDER: If somebody wants to forcibly swab someone against their will or not, or collect someone, from somebody that is unable to, the person whose name is -- that sample has to sign the attestation form.

DR. MAHOWALD: I see. I guess I would again invoke Jeremy's point that he called the person who sends you the tissue to be tested a customer rather than a consumer, and it seems to me that designation would be more accurate.

MR. BENDER: That would be -- yes. Somebody that sends us the sample is the customer, that is correct.

MR. GRUBER: May I address the question?

DR. WATERSON: Yes, you may.

MR. GRUBER: This is Jeremy Gruber.

To address, to follow up on your point following up on my point, I don't think it's at all hard to believe that surreptitious collection couldn't happen in this context. We see rapid adoption of surreptitious collection in the forensics area, so I don't see any reason why there's all of a sudden a firewall between what's happening in forensic DNA and what could

possibly happen in terms of medical direct DTC applications.

I would say that, to my knowledge, just about every DTC company has their own policies and procedures in this area, and I certainly would recommend and encourage that there would be some sort of standardization, including how the sample is to be taken, including the level of consent required. I believe many companies require -- allow for multiple DNA testing kits to be purchased at the same time.

Some companies allow parents to send, supposedly parents, to send in samples of their children. With a lack of regulation, there really is no standardization, so I really would encourage, particularly in that case -- that's one area where that I think we really could come up with a definitive way of protecting people.

DR. MAHOWALD: For example, there could, at least, be on the part of the companies a requirement of attestation about the person from whom the sample is taken.

MR. GRUBER: And I would also submit that much of the information related to this issue is oftentimes not as clear as it can be in terms of where it is on the website in the context of the other types of information it is included with. So I think we have a long way to go to improve in this area.

DR. WATERSON: Yes.

DR. DAVIS: Margaret Davis, Consumer Rep.

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We all in here are consumers, we've all bought something or got some service that we were dissatisfied with. My question to whomever can answer it is do you have some mechanism for consumer complaints if somebody's not happy with whatever happened when they got their test? Is there a hierarchy, is there a process? If it's not resolved to their satisfaction, what next?

MS. GOULD: This is Ashley Gould.

So we have a customer service team, and people just send e-mails or can talk to a customer service representative over the phone if they have questions or are dissatisfied.

DR. DAVIS: And if they're not satisfied, is there --

MS. GOULD: So we have a refund policy that's on our website and, you know, people can always apply to the Better Business Bureau if they're, you know, if there's a reasonable disagreement at the end of the day.

DR. DAVIS: This is across industry, or are you only speaking for yourself?

MS. GOULD: I'm speaking for myself. I can't --

DR. DAVIS: Okay.

MS. GOULD: I can't speak for other people.

DR. DAVIS: All right, thank you.

MR. BENDER: Lew Bender, Interleukin Genetics.

We have, again, a same policy. A person can, if they're not

satisfied with the results, they can certainly speak to a customer service representative. If they want to return the kit, they can return the kit, they get a full refund.

DR. DAVIS: What happens to the DNA samples? Do they get those back? Do you discard them?

MR. BENDER: The DNA is destroyed. It's on our website. We don't hold any DNA. We only analyze 28 SNPs. We consent for that. And the DNA is destroyed within two weeks after we obtain the data, and we tell the customer that.

DR. GALLAGHER: For any of the three company representatives, I'm wondering about disclosure to third parties for the sale of any of the samples or data that you receive. I understood you to say that you destroy your samples, but do you have any other --

MR. BENDER: Unless the customer or the person who sends in the sample requests that this material, the information, go to a third party. We do not. We do not provide any third party that information. It is only between the company and those people who know, and I don't even know the information, I'm the CEO, and the individual and anybody that they prefer to have that information sent to. But they have to send in a signed form to send that information. And we do not sell it at all.

DR. TSONGALIS: This is for Jeremy, Ashley, David, whoever wants to take a crack at it, but when I was in graduate school, Francis Collins

came to give a lecture, and he said the cheapest genetic tests you can do is a good family history, and this has been mentioned over and mentioned again today how important this is.

And so do we have data or do you know, from your clients, whether a family history that I do in an exam room with a provider is more accurate than a family history I give sitting by my fireplace on my laptop with my wife poking me, saying what about your Uncle John.

MS. GOULD: This is Ashley Gould again.

I think that -- I think more studying is required on this subject, but one thing that I'll say is that we have a number of customers who are adopted, they have no family history, so this is an initial lens into their family history. In addition, what we found is people have a lot of assumptions about who they are from an ancestry perspective and that -- and those assumptions can sometimes guide who physicians test for certain things. And what we found through our ancestry services is that those assumptions are often not correct, so that -- that's another way in which this testing can be very useful, we believe.

DR. D'AGOSTINO: Can I follow up on this? It's a question I was trying to get out before.

Is family history built into the assessment you make, these genetic tests, or you ignore all that and just come up with what the genetic profile is?

MS. GOULD: This is Ashley Gould again.

At 23andMe, what we take into account is based on what the underlying published research has taken into account, so where we have age, ethnicity, and those are things that we take into account. It is definitely -- it's actually an ongoing project, where we would really like to do research into adding both family history and environmental factors, things like do you smoke and those kinds of things, but that will require -- we'll need to be very thoughtful in how we approach that, and hopefully, we can conduct research that will aid, so that family history and genetics can be incorporated together in these assessments and more useful.

DR. D'AGOSTINO: In the cardiovascular field, it's been shown in the diabetes that if you have lab values, blood pressure, cholesterol, smoking, behavior, diabetes status, that you don't get very much, if anything, by adding genetic profiles. They have these measures of do you change classification and so forth. Are you doing that type of research? Are you focusing more on the genetic profile?

MS. GOULD: So we've not undertaken that research at the moment, but I think that one of the areas, when we have spoken to physicians that they're interested in learning more about, is whether or not it helps to change behavior, so if you know -- if you also have genetic risk and you're a smoker, does it help knowing that you're at higher genetic risk to help give you the impetus to stop smoking? So the research is not done, but I

think it's an interesting area for research.

DR. D'AGOSTINO: Um-hum. And because I'm familiar, again, with the cardiovascular, where you are now and family history and all that can add something, but your blood pressure, cholesterol, diabetes profile is really going to tell you where you're heading.

MS. GOULD: And I think this was mentioned in previous discussions, but we also very clearly talk about genes and environment, and where environment is more important than family history in these things for diabetes, for example, so --

DR. D'AGOSTINO: Do you imagine, for example, that the diabetes testing might fall by the wayside because there are papers saying that once you know the family history, the glucose tolerance test, you don't get any information from the genetics or -- I mean, we might find new genes, but the ones we have don't seem to be adding anything.

MS. GOULD: I think we might find new genes, right. There could be thousands of mutations that together do confer a risk that's meaningful, but the research needs to be done.

DR. D'AGOSTINO: Thank you.

DR. WATERSON: Dr. Lipkin, you had a question?

DR. LIPKIN: I did. Actually, I had a question for Ms. Gould.

Sorry to keep you.

MS. GOULD: It's all right. It's all right.

DR. LIPKIN: So I'm a clinical geneticist, somebody who actually orders genetic tests and sees patients. So I want to describe two anecdotes of patients I know involving 23andMe.

The first one was interesting. It was a woman who had training in biology, who tested, who did the 23andMe test, and I got actually access to her primary data, which she wanted, and as a result was actually able to notice that she had no variation around the BRCA 1 gene and was able, from that, to speculate that she had a complete deletion of the gene, which, in fact, was -- she had been tested before, but at a time when -- genetic testing did not look for deletions. So that's an example, sort of an interesting example, of something that I think we'd consider a good outcome.

On the other hand, I've also had other examples, a woman who -- excuse me, yeah, sorry. It was a woman, a family who had a mutation in Lynch syndrome, which is a colon cancer susceptibility syndrome. And she had a sibling who said that she didn't want -- she couldn't test positive for this Lynch gene because she had been tested by 23andMe, so she misinterpreted, in other words, the results of the -- you know, the results of the test.

So I guess this is why the committee is here because of the positives and negatives and we're trying to sort of balance risk. But taking a step back and looking at this globally, I think it's sort of like post-market surveillance or the analogy of like drugs, I'm a little confused about what is

done, really, to find out -- you know, I just mentioned these two outcomes and there are hundreds others or thousands, perhaps, that are similar we just don't know about.

So what is -- you know, what is your thinking in terms of for direct-to-consumer testing with -- how can we have adequate post-marketing surveillance to really know what is happening? My understanding, at least, from my speculation or my understanding, at least, from, for instance, drug and device regulation, is that this is often a problem, you know, and that the absence of side effects or problems is not necessarily that they aren't there, but that they haven't been captured in these types of databases.

MS. GOULD: So this is Ashley Gould again.

I think that we are actually optimally positioned to conduct post-market surveillance through -- our service is entirely web-based, and we serve up surveys that are completely optional to take, so we can't force people to continue to give us data, but we do find that people do give us a lot of data, so it's -- I think it's a great area for us to conduct, through surveys, and we can do it through single questions instead of having people take long surveys where they don't want to commit the time.

But we are, already we're starting to do some pharmacogenetic follow-up and, you know, to really -- this could help in the drug area for post-market surveillance for other, for drugs, where people aren't collecting data. We have the opportunity to collect that data so that we can look at people's

genetic information and how they respond to certain drugs, even over-the-counter drugs, and hopefully learn from that. So I think we do need to do more work, but I think we're very well positioned to do it.

DR. LIPKIN: I guess my comment was that there's sort of -- to make the point that there's an absence at the moment of really knowing what happens or -- well, even in the medium term and long term with patients who've had these direct-to-consumer tests and, you know, you hear of some of these anecdotal examples which individually really don't mean very much, but in the aggregate this is important.

So what would you envision, you know, if you had -- if this were to continue, say, just under the current, you know, system, all right, with no change? You know, what sort of -- what should be done in terms of following up these patients to really know what is happening with these tests because at the moment, you know, many of these tests, for example -- and you know, these variants from the SNP arrays, for example, individually have minimal information content.

But this is going to change, you know. We're going to see relatively soon, I think, you know, the advent of, you know, we can now sequence exons for about \$1500 and genomes for \$9500, and on a research setting, this is done. So this is changing very rapidly, and I think we're going to have really more examples of, sort of, like the BRCA and these high penetrance mutations that come out that is the rare variant, you know, rare

variants that have a significant effect.

So what can we do or how should we think about what the industry is going to do to police itself and enable this information to be able to be collected so we can even assess what the risks are?

MS. GOULD: So I think one -- and as I said at the beginning of my presentation, we're working practically with FDA, so we are -- we've hired a regulatory affairs senior director, who you'll hear from tomorrow, so we're taking this very seriously. We want to come under regulation. So I think that it will be part of that process in terms of reporting just like for drugs, to report on significant adverse events, something similar to that.

Now, that would only capture what people provide to us, so I think we'll have to think about if there are other ways we can reach out to people with surveys or have physicians contact us or contact some other, I don't know, independent agency. But I think it's an area we need to think about, but I'm confident we can collect the data to do it.

DR. WATERSON: Dr. Hirschhorn.

DR. HIRSCHHORN: I'd sort of like to follow the same path a little differently. Do you ever get families, so if you get a single person, do you then get the other partner in there, because it's well known by people who do families like you do and like I've done, that there's about a 10 percent incidence of non-paternity.

MS. GOULD: Yes.

DR. HIRSCHHORN: So that -- yes. There also is another thing which is peculiar and that I'll just mention in passing, which is it now becomes apparent that there is considerable somatic mosaicism so that you may find changes between two siblings, two identical twins, et cetera, and I wonder, do you ever follow that up?

MS. GOULD: So non-paternity is distinctly an issue. It's one that we raise in the risks and considerations of undertaking the service, and we have had issues of non-paternity being brought to our attention. It has not resulted in -- I mean, it's part -- you have to understand that it's a possibility and you know -- so that's part of transparency in understanding before you decide to undertake a service like this.

In terms of the differences between identical twins, I'm not a scientist. I don't think, with genotyping, that we can see those differences, but I'm not an expert in that area, so I apologize. I can get an answer for you, though.

DR. LIPKIN: One last tiny -- I just popped in, then I'm done. So -- oh, actually. So this just came back for just a moment and, you know, I'm just thinking of following up. One way, just may rephrase the question, and sort of that way, I think you have potentially bad outcomes. And this, I think, is part of the public record. To date, how long has your company been in operation?

MS. GOULD: The company was founded in 2006, but the

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service was made available in late 2007.

DR. LIPKIN: So about four years, right? Have there been any lawsuits against your company claiming damage that have been filed?

MS. GOULD: There have not.

DR. LIPKIN: There have not. Okay, thank you.

DR. TSONGALIS: So this is for Jeremy.

You know, one of the issues we're dealing with is on the interpretation of the test results and who will do that, and are clinicians or providers capable of doing that, because if you look at our medical school curriculums in the U.S., you measure genetics or exposure to formal genetic testing in a matter of a few hours in the course of a four-year program, which, in my opinion, is completely inadequate.

And so whose responsibility is it to make sure providers can interpret results or clients or customers interpret these results correctly? Is it the DTC company, is it the medical center, is it the family physician down the road? Where is that -- I mean, how do we do this?

MR. GRUBER: Well, I think, at least when it comes to common variants, I think there's an assumption and certainly, there's -- and it's certainly stated by the industry that physicians aren't capable of understanding this information and, therefore, it's important for the DTC industry to be there to provide that service.

I would submit that there's an assumption there that the

information is valuable, that the physician cannot properly interpret valuable information and, therefore, the DTC companies would need to. I would say that in most cases that information is invaluable and, therefore, it's a question of where are we in the process of understanding this information, where are we in the process of developing clinical applications of this -- with this information.

And in most cases, we're just not there yet. I mean, I think the DTC companies, in most cases, are offering information of little to no value. Whether or not a physician can interpret it or not, I'm not sure that that's really relevant for a lot of these, at least in terms of the direct clinical setting.

I would like to see -- I think, I personally think, that many DTC companies, at least the way they currently operate, sort of fill a void that didn't exist. They created their own, sort of, self-fulfilling prophecy by the way they operate, but I'm not sure that they're necessarily filling a need that existed prior to their coming into existence. So I'm not sure that we're really asking the right questions in terms of these issues.

I would like to see, certainly and particularly, because these DTC companies, most of them, they operate on a very reductionist philosophy. They look at your DNA, they make predictions based upon your DNA, but as they've all admitted, they don't look at family history, they don't look at environment.

And as we're coming to learn more and more every day, genes

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are -- and DNA are very complex, and we need to understand how they work in the context of all these different issues, and these companies don't provide that service. They look at one part of a whole, and they leave the individual to make interpretations based upon information that doesn't really offer them a complete picture of what the relative risks are.

DR. GULCHER: May we respond to this or do we remain silent?

DR. WATERSON: Yes, you may respond.

DR. GULCHER: Jeff Gulcher.

I think there's a misinterpretation. We're not suggesting that physicians are not capable of using or understanding this information. In fact, I think I said in my own talk that I think physicians can use relative risk information. And they are the best positioned to define family history, to define all the conventional risk factors, and integrate it together with the purely genetic relative risk information that we are all providing.

So we're not trying to substitute for a physician; we're simply providing a service that doesn't exist otherwise to find the genetic risk, and we help or facilitate the interaction between a patient and the physician to integrate that information.

DR. NG: So I'm struck by this conversation about the history of lab testing in general now being applied uniquely to genetic testing. I'm struck by the fact that there was an article given to us from the Choreal Group and a really nice interpretation of a genetic test related to -- for

diabetes related to body mass index and family history. And when you look at their diagram, the genetic test, which is one down here, has minimal, if any, impact on the prediction whether or not that person's going to develop diabetes.

My question to the companies, my first question is why are you not presenting your data in this way, in particular, relative to family history that we've been talking about as a major predictor of whether or not you're going to develop the disease?

The related question to that, I'm sorry, is a second article that talks about odds ratios in general, and I think the one thing, from my perspective, that physicians understand poorly is how to correlate an odds ratio to a positive predictive value. This article, in particular, talks about if you have a false positive rate of 10 percent or true positive rate of 80 percent, to be predictive, your odds ratio has to be 36, if I understood the article correctly. And what I see, from the genetic testing that you're providing today, nobody has an odds ratio of 36 with the exception of the high penetrance genetic mutations for rare diseases.

So my questions to the companies are would you consider presenting your data this way, in a better context of family history and other related things such as body mass index?

And, secondly, would you present a referent, which is the odds ratio needed to be predictive instead of the odds ratio you're currently

showing, just with an association with disease?

DR. GULCHER: I want to point out that family history is not a great surrogate for the genetic risk of common diseases, and it counts for a very small portion of the genetic risk. It's been estimated that 50 to 70 percent of the risk of most common diseases is genetic versus environment.

So clearly, a patient who has a Mendelian sub-form of breast cancer does not -- and the genetic risk related to that or the family history related to that is not accounting for the vast majority of breast cancer patients who have no immediate family history. They may have a distant family history, but certainly not immediate family history.

And the descriptions that you quoted, the studies that have been looked at with respect to family history, impaired fasting glucose in the context of genetic information, well, those very studies, the study that was published, I think, in a journal from Sweden, showed a reclassification rate of about 15 percent. Patients who were lean, who subsequently developed type 2 diabetes and had no family history, that's where the genetic information has utility.

It's independent of family history, it's independent of BMI, and we know that about 30 percent of type 2 diabetics are actually lean, they're not obese or overweight, and so this is where the utility comes to bear. And I would say reclassification rate of 15 percent is quite significant, clinically.

DR. D'AGOSTINO: There is a very tight population that you're

talking about. I think the question that we're raising is that the genetic testing alone, I think nobody, certainly myself, if I were to close down genetic testing, I would have to retire. So I'm not interested in going that route.

I think the question we're raising is that there's a lot of other information that's the family history, I get over and over again the cardiovascular type of profiles, and we don't see or I don't see them being built in to the presentation, and what's going on in my mind is I want the physician there, but I also have the question are these tests even worth the while, and what is the method, that we really have comfort that we're dealing with things with the genetic testing, is going to add something beyond what we already know. And I think that's the type of question that's being -- that I'm tossing out, and I think the previous question is also getting at that.

DR. GULCHER: And you mentioned the Framingham score is such a great predictor of risk, and I think what you were referring to, the article where you need to have an odds ratio of 30 is so that you can define an AUC or ROC curve that is on the order of 90 percent predictive of a particular disease.

But as we keep pointing out, for the common diseases, you're never going to be in a position where you can determine, with certainty, that a patient's going to develop prostate cancer or the opposite, where you can define patient's risks so low that he's completely immune from prostate cancer.

We're never going to get to that position, and I think that is what -- I mean, fortunately, the cardiovascular disease, we have many different risk factors that conspire together to define a fairly large ROC curve, but we're not there yet with prostate cancer. We don't even have conventional risk factors for prostate cancer other than family history and ethnicity.

And as you saw from the ROC plots from the Gail score, which -- the widely used Gail score from the NCI, from Mitch Gail, you realize that the AUC curve is only about .6 with that and the JAK markers further enhance that, but we're nowhere close to where we are with cardiovascular disease. But yet, you can define patients who are at higher risk than average, twofold, threefold, and are you going to do something different about those patients or not?

DR. LUBIN: So I think one of the pieces that we're missing from the way this data's presented is that doctors may be able to make decisions, but they need to be given the information from which to base their decision, so the focus has been on genetic risk, but there's also information in terms of population based risk, risk that's conferred by other means, such as what we've discussed as family history, which, I believe, is often not presented on these kinds of reports. The genetic risk may be significant in itself, but in terms of overall risk for the condition, it may be very minimal and, therefore, not be useful.

The other -- so that's one comment I wanted to make. And then the question that I'll ask is what thought has gone into expanding the reports to make sure that the physician has this information?

Before addressing it, I want to make one other point, and that is while family history for common diseases for about 10 percent of individuals is a very powerful tool, and for a larger percent of the individuals, there is still a genetic component that's largely unknown.

So having markers in which you have relatively small odds scores associated with a condition, I believe for the majority of conditions, have not yet been proven to be predictive for that condition, and we don't have -- I would say that we don't have enough of the genetic picture to really be able to make solid predictions for the majority of the common disorders that are reported out there at this time.

So there's two questions. One is thinking in terms of the totality of information that needs to be provided to the clinician in addition to genetic risks so that an informed decision can be made, and also the question of dealing with markers that have these small odds scores and even less information about the predictive value in making some conclusion.

DR. GULCHER: Thank you for the question.

So when it comes to the integration, and I really think it's the physician that's the best position to integrate this information, but as you suggested, we do offer tools for physicians, not to the individual patients but

to the physicians, to actually catalog Framingham score, to take family history and other risk factors for the Gail score and show how that information would be collected through web interface by the physician based on the patient's information and integrate the overall risk or define an estimated overall risk which accounts for the genetic risk plus these other conventional risk factors.

When it comes to this concept that all the variants that we are producing have minimal relative risk or odds ratios, as you keep talking about, we combine risks from individual markers. We are not presenting a carrier status that you're very familiar with when it comes to Mendelian diseases. What we're doing is we're integrating whatever validated risk markers, individual risk markers, integrating the relative risks together.

And this rare confluence of common variation, in some cases, actually defines very high genetic risk indeed, as I showed you with prostate cancer and breast cancer. And that information is independent of the conventional risk factors that are being cataloged by physicians including family history so far.

But as you point out, there is a large amount of missing genetic information, no question about it. But the era of common variants and GWAS studies is essentially over, right? Now we're doing full sequencing of genomes in hopes of defining some of the structural variation or some of the lower frequency variation that have high individual effects. And that will complement the common variants that we've already found.

The common variants will not become obsolete. They actually do contribute a fair amount on the population-based level to risk. As we published yesterday in *Nature Genetics*, this -- we're sequencing the entire Icelandic population over the next 10 months by sequencing 2500 Icelanders and using family-based imputation through our phase chromosomes to derive sequence information, full sequence information, not just exonic sequence information from another 300 or 400,000 Icelanders down to at least a point, frequency of .1 percent, but our first dive into that has already revealed low frequency variants, as you might predict, that have very high effect, indeed, on common forms of common disease.

So we defined a variant that has about .4 percent allelic frequency, and it confers a 12.5-fold risk for sick sinus syndrome, which is the most common cause for cardiac pacemaker placement. So we're already getting a glimpse of that.

But the question becomes is the information we already have, that we've already discovered, for some diseases, are they useful for reclassification or for prediction or not? And I would contend that there's already clinical utility data that suggests that there are substantial predictability beyond the conventional risk factors where that, in some cases, may be useful to a physician. In other cases he may want to wait until there's additional genetic information known.

DR. RANSOHOFF: Jeff, in several of your answers, you've

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referred to the clinician as being the one to do the integrating of the data and we heard from Jeremy that this is -- the genetic data is reductionist, and Greg has talked about who should do the interpretation, and who does the interpretation has been a part of your answer and everybody's discussion recently.

And I think people aren't arguing that there isn't information there, it's just that it's complicated and it may need to be integrated with other stuff. With that in mind, can you say more about where you think information, just to the consumer alone, is okay or how that fits?

Because I think, I don't think people are arguing that there isn't information there that a doctor, somebody trained adequately, can use, but a separate issue is if the information's there and it's complicated, sometimes it's subtle because of low odds ratios and so forth, who should do the interpreting?

DR. GULCHER: Yeah. So we're not asking the consumer to interpret odds ratios of individual markers. None of the companies are doing that. They're actually -- they're combining the information together using a standard model, and they're giving the bottom line information, like you see with 23andMe. They show what's your potential lifetime risk, if you have this genetic profile, versus the average population for that particular disease.

DR. RANSOHOFF: So it's the companies?

DR. GULCHER: I'm sorry?

DR. RANSOHOFF: It's the companies doing the integrating?

DR. GULCHER: That's right, yeah. We're not asking physicians also to combine the 25 different markers in their head on -- they can certainly do that. They can actually simply multiply the relative risk conversions that we already have and we show that in the report, but they don't need to do that because we also give them the bottom line, what is the relative risk of the patient developing breast cancer compared to the general population, and then we give an estimated lifetime risk only as a way of reinforcing that some diseases are much more common than other diseases.

DR. RANSOHOFF: So it's an issue on the table, then, can a company do that or can something on the web or whatever it is, totally separate from a doctor, is that --

DR. GULCHER: Yeah.

DR. RANSOHOFF: -- an issue on the table?

DR. GULCHER: So that's what we're providing. We're not providing the individual results and requiring either the patient -- consumer, sorry -- or the physician to combine the information. That is done for you in a transparent way where all the companies describe exactly the methodology that we use to combine them. You could do it yourself by hand.

But the important thing is we're giving the information in a way that we hope is understandable by a patient, and you could make the argument that relative risk is not very understandable. We convert

everything from odds ratio to relative risk because most physicians don't know what odds ratio is.

DR. RANSOHOFF: Should the product, then, is here's some genetic information plus your family history plus other features of environment and so on and so forth, and that's what the company or a vendor or somebody is saying, we're going to integrate that all together?

DR. GULCHER: No, no, no.

DR. RANSOHOFF: Not just genetic information --

DR. GULCHER: No, no. I --

DR. RANSOHOFF: -- just the interpretation.

DR. GULCHER: -- thought you were talking about just the individual genetic markers that we have for particular tests. The integration that we do, we do on a limited number of diseases, afibrillation using the Framingham major fibrillation score, myocardial infarction risk using the Framingham myocardial infarction score, and the Gail score.

And there are a limited number of scales, as you know, that are validated to allow one to actually do this in a very careful way. Even if you look at family history, you just keep -- on the family history, you realize there are no good summaries of what the relative risk is if you have a father who has prostate cancer or if you have a father who has Crohn's disease. It's just -- there's a wide variety of different studies, and they all come up with different conclusions.

So what is the validated term that you would use, what would be the validated relative risk that we should use to satisfy the FDA when we're trying to integrate that together with additional risk factors. And I would contend that it's probably better to let the physician provide them the tools to do that themselves.

DR. MORIDANI: In my perspective, relative risk and absolute risk odd ratio are generally misleading. As part of your report, do you provide the information on prevalence or how many people per thousand subjects are -- or ten thousands are affected because then, in that case, odd ratio -- basically means almost --

DR. GULCHER: An odds ratio of 10 for a disease that has a prevalence of .1 percent also is totally useless in an asymptomatic patient. But when it comes -- but an odds ratio of 1.5 may indeed be quite useful when you're defining a patient's 10-year risk for myocardial infarction because it may classify them into the higher risk category, the NCEP defined categories of risk, and it has a big impact on whether or not the patient should be treated more aggressively and have a lower, perhaps a lower LDL cholesterol target. So you're exactly right, prevalence is important in defining what the absolute risk is, and that's what all the companies do.

DR. MORIDANI: So you're not providing it as part of your report?

DR. GULCHER: That's right. And most of the companies

annotate the actual epidemiologic study that defines that lifetime risk for afibrillation is X, right, because they're obviously different. You can't get a group of epidemiologists together to agree on a particular estimate or which study is the best, and so the companies tend to pick the one that has the biggest, largest outcomes.

DR. WATERSON: I'd like to end the discussion now, if we could, and -- okay. We're just going to close the public hearing session at this time, and I'd like to recommend we take a short break and going to reconvene at 3:30.

(Off the record.)

(On the record.)

DR. WATERSON: At this time, we need to focus our discussion on the FDA questions. Copies of the questions should be in your folders.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak and because it's difficult if there are multiple conversations going on at once. Please try to limit that.

Dr. Elizabeth Mansfield, Director of Personalized Medicine Staff from the Office of In Vitro Diagnostic Devices at FDA, will present the FDA questions.

Dr. Mansfield, would you please read the first question?

DR. MANSFIELD: Yes, thank you.

For any of your reference, there are shortened versions of the questions on the slide behind you, so you may refer to those.

The first question we would like the Panel to discuss today concerns: What are the risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician?

The first part of the question is: Direct-to-consumer tests are offered to a mixed population consisting of symptomatic and asymptomatic individuals, with or without known family history of disease, with varying demographic features, and with varying access to medical expertise. Please provide your assessment of the following questions using the specific categories of tests listed below as examples.

And I will direct your attention to the table in your questions. There are five categories: carrier tests, pre-symptomatic tests, susceptibility or pre-dispositional tests, pharmacogenetic tests, and nutrigenetic tests. In addition, there should be, in your Appendix 2, a long list of the types of tests that may be offered under these categories. So I'm going to go back to here.

So, Dr. Waterson, would you like to address each of these sub-bullets one at a time or would you like me to read them all at once?

DR. WATERSON: What do you think would be the best way to approach it, would be most helpful for you --

DR. MANSFIELD: Let's start with the first one. So please

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discuss the following: Is there value, considering likely benefits and risks, in offering clinical genetic tests directly to consumers rather than through more traditional means?

Should any of the categories -- and that is the five categories I demonstrated -- or specific genetic tests listed below or -- whoops, I went past the first question.

So -- okay, you want me to keep going? Okay. Is there value, considering likely benefits and risks, in offering clinical genetic tests directly to consumers rather than through more traditional means?

Dr. Waterson, you can --

DR. WATERSON: We'll let the Panel members comment.

Dr. Hersch.

DR. GUTIERREZ: Can I suggest that we take each category and walk through each category on its own? So start with that section. Is there value for carrier tests?

DR. MAHOWALD: Could I just -- on the -- this is Mary Mahowald.

On the question sheet that we got, the question is in your opinion, is there net value, and to me, there's an important distinction between net value and value. I could rather readily identify some values, but net means I'm weighing that against risks. So which do you want? Do you want net value or just value?

DR. NETTO: And why are the two sheets different? Why are the questions we got different than the question we just got now?

DR. GUTIERREZ: Well, one was in the package. Should we not go with the latest --

DR. MANSFIELD: Yes. I'm looking at the package. It was net value. Looking at the screen, it's just value.

DR. GUTIERREZ: Mine just says value.

MR. SWINK: Okay, the Panel pack was sent out a month ago and that was -- those questions have been updated, so use the questions in your red folder.

DR. MANSFIELD: Oh, yes. I'm sorry. We made some slight updates to the questions after we sent them to the Panel.

DR. MAHOWALD: So you don't -- the question is not about net value, then?

DR. MANSFIELD: Although you may opine on net value, if you choose to.

DR. WATERSON: Follow Dr. Gutierrez' suggestion, and I'd like comments first on the carrier testing.

I guess, as a practicing clinician, I don't see much risk associated with obtaining the carrier testings. They may provide some valuable information, especially when used, perhaps, in a prenatal context.

MS. HOUSE: Hi. Tiffany House, Patient Representative.

I do have a question about the carrier testing. I mean, I know for my disease, Pompe, that it's not all of the mutations are even known, so is there a danger that carrier testing for only the more common mutations, you know, a patient is going to get a report that says you don't have the common mutations and then think that they're not a carrier but, in fact, they are.

DR. WATERSON: Dr. D'Agostino.

DR. D'AGOSTINO: Yeah, we had a long discussion going back and forth about family history and risk factors and so forth. These tend to be, in my understanding, cystic fibrosis and -- diseases which I'm quite familiar with, you basically have it, yes, the gene, yes or no. It's not a question of things are going to -- it's going to improve by a plethora of other demographic variables. I mean, if that is true, then I agree with the statement you made.

DR. MANSFIELD: Carrier testing is typically for Mendelian disorders.

DR. D'AGOSTINO: Right.

DR. MANSFIELD: So where the penetrance is relatively high.

DR. SHAMBUREK: Yeah, I mean, I think in a pure world, the correct results and interpretations will give you peace of mind and it can be involved with family planning and other things, but I think we heard, for instance, with cystic fibrosis and maybe Pompe disease, where if you're told, if you get the one where there's eight screened, genes screened, or 25, you still may not be certain and it's inaccurate unless there is some way of

knowing you're being updated or you're reassured.

So I think it can affect family planning and knowing your potential treatment options and the limitations. So I think there is some risk.

DR. WATERSON: Yes.

DR. D'AGOSTINO: I think the questions are asked backwards.

A-s-k.

(Laughter.)

DR. D'AGOSTINO: The third question is about the validity of the tests and so forth, which is so important. I mean, do you have a test that really works and so forth, and we sort of saved that for the end.

I'm responding to this one by yes, we do have a test, but I agree 100 percent that if we don't have a valid test, it's a different game altogether.

DR. WATERSON: Yes.

DR. HIRSCHHORN: May I just --

DR. NETTO: Yeah, sorry. I think we're making the presumption that all DTC administered tests are going to be in CLIA-certified laboratories, and even with you're saying okay, it doesn't cover all the mutations, but that's even in the best of hands, CLIA. And when you're offering it through DTC, there is no way of knowing that some patient is not going to get that false negative reassurance as a carrier with a test that's not meeting even the optimal standards that are standard of care right now, so that's very concerning to me.

DR. HIRSCHHORN: I'd like to really focus on that because there now are increasingly reports in the literature, case histories, in which they have identified, in the affected, a mutation, a known mutation on one allele and have not as yet identified the mutation on the other allele, and that would be carrying a carrier who would not be picked up by this testing.

And I think, especially in the disorder that was talked about just now, Pompe's disease, where you have a therapy, to miss something like that is really a significant thing.

And I think that's true of more and more diseases now, you know, like the Tay-Sachs where there's a paper very similar to that, particularly, which is very important because we used carrier identification for Tay-Sachs to wipe out most of the Tay-Sachs in the Jewish population. And what you're left with now are mutations of Tay-Sachs that you've never seen before. So you more and more have instances where you don't know where the carrier is.

I didn't put myself clearly, but I think it's very important to do that. Okay.

DR. WATERSON: Gregory.

DR. TSONGALIS: So I think the discussion just highlights the importance of either the consumer, the provider, or a counselor really understanding the genetics behind the disease in carrier testing and all of the risks associated with that. The other thing that I don't think we should under-

estimate is with carrier testing, the ability to identify non-paternity.

DR. WATERSON: Steven.

DR. LIPKIN: Thank you.

Someone who has actually seen all the patients that are listed in this category, you know, sometimes the cases are straightforward. But a lot of the time there are wrinkles that come in and a lot of complexity, and because a number of these disorders, you know, you're talking about fairly serious issues involving potentially abortion or involving, you know, in vitro fertilization, and these are big decisions and they're complicated.

I personally feel uncomfortable with offering these tests, which have historically, actually, been really provided by medical professionals. Doesn't have to be a geneticist. We're talking about nurses and such, and there are lots of opportunities for this. But this information, if misinterpreted, can lead to, once again, lethal outcomes, and that disturbs me a lot.

DR. BOUGHMAN: Joann Boughman.

I would remind us that along with the test in the laboratory that's being done, there are professional guidelines about the most common alleles, the general recommended panel in various populations, and medical professionals of all types would understand that the two would go together for a complete interpretation of the test. And I think it may unreasonable to expect any test itself to include the medical guidelines or the professional

guidelines that go along with the interpretation of every test. But a medical professional would know how to put those two things together.

DR. WATERSON: Do you feel that it should go through, primarily through, a medical professional to get the initial test, or wouldn't people, if they got a result, wouldn't they go to a medical professional or a prenatal diagnostician or whatever to get the rest of that information filled in, like testing the partner, whomever, might need to be tested?

DR. BOUGHMAN: They may well go to a practitioner afterwards, but if, in fact, it is going to require the intervention or the inclusion of a practitioner in the process of getting the test, interpreting the test, and acting upon the test, I'm not sure why Step 1 would not be a part of that process.

DR. HERSCH: Question.

My conception of most carrier testing is that it happens around pregnancies or considerations for pregnancies, so the idea would then be instead of working through your obstetrician or referral to a geneticist, you would do it yourself. Is that actually practical or is there -- would there be a demand for accomplishing it that way and is there a reason, I think, that there's a benefit to do it that way versus the alternative?

I don't think people really think that much about oh gee, I want to find out my carrier testing. It's just that maybe some carrier testing would be included in some of these bigger panels. Is that more why it comes up?

I'm a little bit at a loss as to why this would be specially sought as a DTC.

DR. WATERSON: Greg.

DR. TSONGALIS: So I think one of the other exciting things about DTC and exciting in a good/bad way, I'm not sure, is that we have listed here very well characterized diseases with known mutation spectrum, with known clinical guidelines. But, again, one of the exciting things about DTC is that we enter a brave new world where we do carrier testing for things where there are no guidelines, for things that we don't know what the full mutation spectrum is with respect to a lot of these diseases that we saw listed today. And so that gets to be a little bit tricky on who does this and how that information gets conveyed.

MS. HOUSE: You asked about why maybe somebody would bypass a doctor to go directly, and my concern doesn't mean that I necessarily think that it shouldn't be available. I know patients who, you have a patient that has Pompe disease and their partner doesn't know if they're a carrier and they possibly want to consider having children, and their doctor refuses to test the partner because it's so rare that the odds of you being a carrier are almost nonexistent, what's the point.

Well, you know, that's kind of a ridiculous response if you already have one person with it. You know, the partner should be able to find out. And so in a situation like that, even finding out that you don't have the common mutations might be a little bit of help. It's not as much help as I

think you need, but it's a step.

And I think that, in my opinion at least, it's not that I don't think the information should be available. I think that it needs to be disclosed very, very carefully in language a patient can understand what exactly they're getting. So in the case of the Pompe mutation where you're just screened for probably the most common mutations, disclose that. Say this is what we're screening for, this is what you're getting. It's not definitive, it's not 100 percent that you're not a carrier, but this is what you're getting.

DR. WYNE: I just wanted to make one comment about what you said about doctors screening because we have patients who are heterozygous familial hypercholesterolemia, and we take the position that we want to screen their fiancée before they talk about any setting a date, and that's actually a fairly common disorder, so I would look a little bit differently than that physician does on that subject.

On the issue of DTC carrier tests, I think part of it has to do with the type of a test, whether you're doing a Huntington's test or a cystic fibrosis test and, what is it, over 1300 known mutations in cystic fibrosis, but we don't test for all of them when we send it to the lab. So that's the problem is the person who's just buying the result and getting it, how can we adequately ensure they understand that it's not an absolute test?

And you can put anything you want on the Internet or on a piece of paper, but then when it turns out they do have the disease, they're

still going to come back devastated by having a disease they thought they didn't have. So I have big problems with people being allowed to just go order a test and think they're disease free.

I think one place, one issue, to raise though is the person who wants to be tested for a known family mutation, and I get a lot of questions on that, and that's a challenge for me because if they're my patient, then maybe I can send them for that genetic testing. I usually try to convince the family doctor who diagnosed the other family member to do it. But I would raise that as something that is a reasonable test in a lot of situations.

DR. MAHOWALD: On the issue of carrier testing, sort of, another side of what you were talking about, Tiffany, is the possibility, which I've come against sometimes, but in carrier testing, I'm thinking here of sickle cell as well as cystic fibrosis.

Situations arise in which, because these are often associated with reproduction, in which a woman who is already pregnant wants to be -- knows herself to be a carrier, wants to have PGD or wants to have the fetus tested, but it won't be done where it's refused by a medical practitioner because there's no partner available to be tested or the partner will not be disclosed or they don't even know the partner, because the test is only going to be most meaningful, obviously, if we could test both partners.

And so I know situations in which the test has been refused for the woman. So I suppose one could say a value of allowing carrier screening

in that case would at least give information, not fully informative, to the woman that she might not have available through a medical situation.

DR. NETTO: But in both of these examples, what's the harm of keeping the physician, even the primary physician, in the loop advising that patient? I mean the issue is why exclude that doctor to specify in these specific situations where insurance refused or --

DR. MAHOWALD: Well, I'm talking about a doctor's own refusal, so nothing would be keeping him or her. But because the test would not be as informative in terms of the pregnancy, at least some doctors have refused.

DR. HEJAZI: Hi, Shahram Hejazi. I'm the Industry Representative.

I wanted to provide more of a general framework of some of these questions. It seems to me that we've started from the right place, that is to ask a question of safety and clinical validity, but we are tending to creep toward the question of any risk or clinical utility, which I don't believe it's a right framework of the questions.

In answering those secondary questions, which I don't think is really what we should discuss, we are at least suggesting that the providers of DTC are now -- also have some responsibility in providing some healthcare advice with all the information that's available out there.

Now, I do agree that the companies cannot make any

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unfounded or unvalidated claims about what they provide, but I seem to have difficulty with agreeing that, or at least suggesting that, these companies are responsible for any type of healthcare advice or interpretation where the data may not even be available to them. So in order to address the right question, I would go back to try to frame these questions with respect to safety and the clinical validity of what we're trying to discuss.

DR. LUBIN: So there's two ways that we can look at this. One is if we can define a means by which tests can be offered direct to consumer in which there is a reasonable means by which a consumer would understand the results that could drive them to making, to taking actions that improve health outcomes. I think that's a noble direction to go in that kind of category of testing and the elements would need to be defined.

But testing is complex, and if any one of these categories, I think it's very challenging to make conclusions that cover every test, for instance, under the category of carrier testing. For instance, about a week ago there was a discussion I was involved in about cystic fibrosis, and essentially, the way the discussion went was that cystic fibrosis does not cover a single presentation but there's variation, significant variation, in how that disease manifests. There is severe disease in which the life expectancy now, with what we can provide in terms of medical intervention, is in the low thirties, and there's mild disease which can pretty much be managed throughout one's lifetime.

And laboratories today, there is a recommended panel from the American College of Medical Genetics for 23 mutations which are associated with severe disease. Laboratories, you'll be hard pressed to find one that will offer less than 30 mutations, and many, far more, that cover a whole range of presentation of the condition, and the challenge is that in defining someone as a carrier, say, from a laboratory that offers a large panel also needs a consequent explanation of, if known, and a lot of the -- what we call phenotype/genotype association is not known, how that disease may manifest.

So the risk is presenting that kind of information directly to the patient without the opportunity of really being able to explain and have the -- I should say the client understand what does that particular mutation mean in terms of how outcomes may potentially lead to termination of a pregnancy where it may not be indicated, and we just really don't have the kind of data we need to really know how to best handle this information when presented to consumers.

So the point that I wanted to make is that if there are a category of tests in which the risk and the information that needs to be communicated to consumers can be clearly defined with the likelihood that it is safe and can lead to some action that is of benefit, I mean, that's one category, but then you have many disorders that have a spectrum of presentation that cannot be well communicated outside of clinical

consultation that I think we really need to be careful about.

DR. D'AGOSTINO: So are we suggesting that the whole class of carrier tests should have medical supervision, or are we suggesting there are sub-classes where some do and some don't?

DR. LUBIN: It would be very tough.

DR. WATERSON: It's difficult to go through a whole list of diseases and make a yea or a nay --

DR. D'AGOSTINO: I'm exactly with you. I think it's an up or down, and you know, I want to know if that's what you're thinking.

DR. RANSOHOFF: David Ransohoff.

But if it's -- it really is difficult then, you know, what we're hearing in this discussion is complexity, and different carrier states and different diseases may be different. And it scares me to death to think that at the end of today or tomorrow we're going to make some blanket recommendation about all of these things to the FDA when we're identifying all this complexity here, and I wonder if we can retreat a little bit and think about a process.

I don't know if it's an FDA process or a professional society process like EGAPP to think -- you know, if we're thinking clinically, we have to go through each one of these one by one and think about what's the test, how accurate and reliable, is there an intervention, how does that relate to outcome, it's the kind of thing that the U.S. Preventive Services Task Force did

when, 20 years ago or 30 years ago, they deconstructed the yearly physical exam.

That was what was on the left-hand side, the category, yearly physical exam, there were lots of components, taking blood pressure, tonometry, listening to the heart, chest X-ray, all those things, and there was no short-cut. They had to look at evidence for every single one of those things and decide, and what I'm -- I'm not a geneticist, but I'm hearing an awful lot of complexity for all of these diseases, even in the box on the right where we thought it might be simple, and I don't think we can make these on the fly, and I'm just wondering if there is some larger process that this committee or the FDA can think about, and what's its stance related to a professional organization like EGAPP or the task force. I'm not sure what is in what's airspace.

And this question may be out of bounds, but if I'm thinking about what's best for patients in the long run, just as a clinician, I want to know what am I going to learn, what choice am I going to make about intervention, what choice are they going to make, and is that going to benefit them or hurt them? How do you think through that process? I'm not sure who governs that, but that's the process we've got to do.

DR. WATERSON: Go ahead.

DR. SHAMBUREK: One of the issues I think the way I see it, and, again, it's a different framework, is that in the case of drugs which are

prescribed, a case of the H2 blockers or decreasing acid, we had those where it's prescription, we found out which patients benefitted it, and over time and experience and increased data and scientific validity, we could determine safety and in what cases a patient can get, and then that's a case where a prescription has gone to an over-the-counter.

I think we're at the inference of 10 years, maybe five years, before we know what can go -- there are clearly cases. People are expanding on cases now that probably could, but we have to presumably define some guidelines where there are very good companies, truthfulness could be, say, we have validated 28 alleles which will describe cystic fibrosis, and that's truthful, but it does have great limitations because the biggest truthfulness is a black box saying well, but you may be missing some.

DR. WATERSON: Emphasis should be on what we can do, not what we can't do, necessarily.

DR. RANSOHOFF: And the concept is caution first, and then when one gets more experienced, then say at least that's the analogy from drugs.

DR. MANSFIELD: Are we ready to move to the next category of pre-symptomatic tests? I'm sorry. We'd like to get through this first question today, if at all possible.

Go ahead, Alberto.

DR. GUTIERREZ: Yeah, let me just make a comment because I

think Dr. Ransohoff was right. We're not asking -- the Agency at this point is not looking to clear or approve any one of these specifically, and it's not putting in front of you the evidence to say cystic fibrosis to go over the counter.

So we're more asking for general concepts that will allow us to determine whether it is possible to move ahead with some of these or not. I think we've gotten some good discussion that tells us areas where there's benefit and areas where there's risk and the fact that we may have to deal with each disease separately. That is something that we would have to do anyway, so I think what we're looking for is a discussion like you're having.

DR. D'AGOSTINO: We've been told -- I've been doing FDA advisory committees for a number of years, and we're told over and over again that the discussion is the most important part of the process. We don't have any votes here, it's the discussion, and hopefully we're giving you more than enough.

DR. WATERSON: Okay. I guess, for the carrier testing, I'm getting the sense for the committee is that this, for the time being, might continue to be under a physician's or a nurse's purview to order the testing, but as we gather more experience with this, this may be something that we would be more comfortable at switching to the over-the-counter type of a test.

DR. MANSFIELD: Okay.

DR. WATERSON: I think the concerns that we have are some of the limitations of the carrier testing and persons understanding that this testing is not going to be 100 percent correct and there's going to be a lot of complexity even within a given disease as to our knowledge about what the genetics may predict and what it may not predict.

Does anybody have anything they want to just to add to that?

Gregory.

DR. TSONGALIS: So my concern with that is that some of these companies or laboratories have the capability of providing very, very adequate genetic counseling services. And if that's the case, those counselors typically know more about the disease and the genotyping than most clinicians and other people in the healthcare field. So I would, with the exception of places that can provide that type of service, say that a generalization is really not correct.

DR. WATERSON: Okay.

DR. NETTO: My concern, though, is you don't know who all the players are and you don't, by even a token, direct to consumer, you don't know that that patient's going to go to these three acceptable or five or ten that are meeting the standards that otherwise a physician will refer to that lab because the physician knows we only send it to CLIA-certified lab or a lab that I trust the results. And that judgment, I think, is very important and why I think still need to be tied to a professional.

DR. WATERSON: All right. Tiffany.

MS. HOUSE: I think that that's kind of one of the most important things. I think that we can recommend regulating the laboratories and who can do the testing and also leave it open that good companies, that the patient can go to them, you know; why can't we have it both ways? Regulate the companies and what they're able to do, make sure that what they're providing is good, easy-to-understand information to the patients that makes it clear what is and is not being provided, and at the same time give the patient the choice.

I want this information, and if my doctor won't prescribe it for me, then I should have the right to get it any way I can. Because in my experience, there are some doctors that won't prescribe the tests, and so while there are many that maybe will, for those that have no other option, should we really close the door to them?

And, again, my concern isn't with the test, per se; it's how it's relayed to the patient. And I'd like to see maybe the patients involved in the process more, make sure that when the companies are creating the reports and such, that there's good feedback so that it's clear that what they're reporting is what's actually being understood by the patients and, you know, safeguards like that and, again, making sure that the laboratories are doing things correctly than completely closing the door to the patients.

DR. GUTIERREZ: Just to clarify, what's not on the table right

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now is whether these companies will be regulated by the FDA or not. The FDA said that they would. So the quality of the testing, itself, you can assume that it's going to be regulated with one way or the other.

What we want, advice, and this is part of the risk and benefits, so what can you foresee going direct to consumer, if there are some ways to mitigate the risk like providing genetic counseling, and some of the questions will get to that more, but the idea whether the companies are going to be regulated by the Agency or not, I think, is not on the table.

DR. WATERSON: Okay, all right.

DR. HERSCH: I'll just respond to you, if I can. This is Steve Hersch.

From my experience in Huntington's disease, there are occasions, and not that uncommonly, where patients have a desire for a test and would go ahead and get it and -- if they could, and could regret it. And then what we see through the process that we have, which is first educational, is that for some of these individuals, the more they learn about the test, the more they have a chance to decide maybe it's not in their interest to get that test.

And if you take out that interaction with someone who can take them through the risks and benefits, then the chances of folks being able to just write a check and get that test and not have that interaction to better understand the risks and benefits, that won't happen, and so there's more of

a chance for harm.

DR. WATERSON: One more comment, and then we'll move on to the next.

DR. WYNE: I find it interesting that you're actually just now referring to a test that has a lot more ambiguity associated -- a lot less ambiguity associated with than most of the tests we're referring to because so many of ours, like we say, we're only screening the most common mutations whereas with your Huntington's, you're fairly confident of the result that you're giving the person, but it's very clear that counseling needs to go with it. And the idea that the companies have very good genetic counselors available, absolutely that's true, but what did we hear this morning, that a very small percentage of the people actually access that resource, so we can't assume that they're going to have that kind of genetic counseling.

I think the problem comes down to the fact that the tests aren't black and white in most cases. In other words, telling you you're negative doesn't really mean you're negative, and you need to know and understand that, and unless the companies had a way to have 100 percent genetic counseling, we can't assume a person will have proper understanding of their result.

DR. WATERSON: Thank you very much. I'd like to move on to the pre-symptomatic.

DR. MANSFIELD: Okay. Let me again read the background because it's very important for each question: Direct to consumer genetic tests are offered to mixed populations consisting of symptomatic and asymptomatic individuals, with or without known family history of disease, with varying demographic features, and varying access to medical expertise.

At this time, please comment on: Is there value, considering likely benefits and risk, in offering clinical genetic tests directly to consumers rather than through more traditional means, for pre-symptomatic tests?

And by this, we mean those tests that are offered for diseases that tend to be highly penetrant but do not appear until after childhood, such as BRCA 1, such as Huntington's disease and so on.

DR. WATERSON: Go ahead.

DR. MORIDANI: This is Majid Moridani.

Regarding the carrier tests, I had a mixed feeling. I think I can see both ways. But regarding this asymptomatic person, I think it has to remain as prescription only because there is no need to do a screening of general populations regarding something that is not happening. So that's my feeling is that, you know, for people who are not affected, there is no need in a perspective to -- you know, to offer these tests to DTC. And I think it still needs to remain as prescription only.

DR. WATERSON: I think I agree with Dr. Hersch. I think for some of these diseases, I think the educational process is very important --

DR. HERSCH: Yeah.

DR. WATERSON: -- concerning whether you want to be tested or not.

DR. HERSCH: Yeah, I think it's -- I certainly believe that doing Huntington's disease without counseling would be a grave mistake. We get calls not infrequently from people who have had the test done through their PCPs or through folks that didn't really know how to handle the information and they can be -- and those calls sometimes come from people who got the test and some are from the clinicians, and they are often distraught or in a crisis of what to do now.

And the answer from that test is really -- you think something like Huntington's would be really straightforward, but there's a huge amount of nuance in both the considerations for whether the test, for a patient in deciding whether the test is for them or not, and then nuances in how to educate individuals about the results of that test, what should they do with that information and the implications for those results for all their family members and insurance and health insurance and their families. There are just enormous implications.

And if you try to dial back and say well, maybe there are diseases that aren't quite so dramatic or so devastating, it's -- I think, in some ways, it becomes even harder to know what to say when things can be less clear, but so anyway, I certainly believe strongly that pre-symptomatic testing

really requires input.

DR. WATERSON: Dr. Mahowald.

DR. MAHOWALD: I do think there are some differences here, though, and one of my concerns in terms of pre-symptomatic is the lead-ons that -- and that this pre-symptomatic testing ought, certainly, when it's done, to be the decision of the person and so children who could, as a matter of fact, be tested for BRCA 1 or Huntington's or whatever, I would certainly argue that they ought to be precluded from the availability of tests through their parents being the customers until they could make their own decision, that's number one.

But I do think that there are some pre-symptomatic tests that may be offered to adults without the intervention of a clinician, and although Nancy probably disagrees with me, I think, for example, BRCA 1 and BRCA 2 in a family where there are multiple members who have been affected is not an unreasonable option.

DR. SHAMBUREK: Bob Shamburek.

I mean, I would agree if you have a genetic test that show the mother and the grandmother have the positive, that's kind of the exception but if you don't know about the mother and the grandmother, and they're dead and the person gets the test, I'm always worried about the reassurance then, you don't have it. But, in fact, you may do less screening, less vigilance on that or other disorders and get an unrealistic reassurance. So, you know,

it's still we don't know a lot. We're learning a lot, but we don't know a lot, and I think that's my biggest anxiety.

DR. LIPKIN: So I and many others have published on the specific issue of missense variance. So, you know, what you're describing is a nice, once again, like something from a textbook, but, you know, that's one -- that's generally the exception rather than the rule. So, you know, a lot of these patients who get these kind of complicated things -- some things have never been seen before, you know, a truncation, the protein that deletes the last three amino acids. What is that? Tell me. You know, is that a mutation or is it not? It can be hard to know. There is no answer to that.

Or at least I -- well, anyway. So the point is that for many of these cases, there is a lot of subtlety and I think there's -- I personally would be concerned about people sort of having a sense of false security or thinking that they don't have to worry about things and misinterpreting it.

DR. MAHOWALD: On the other hand, for those who test positive, it certainly motivates preventive behavior very strongly.

DR. WATERSON: Okay. Are there any other comments?

(No response.)

DR. WATERSON: So I'm getting this sense from the Panel that we still believe that the pre-symptomatic tests ought to be under the direction of a healthcare provider.

DR. MANSFIELD: Okay. No additional comments? Are we

ready to move forward?

DR. WATERSON: Yes.

DR. MANSFIELD: Okay. Again, considering the direct to consumer tests are offered to a mixed population consisting of symptomatic and asymptomatic individuals, with or without known family history of disease, with varying demographic features, and with varying access to medical expertise, please comment on whether there is value, considering likely benefits and risks, in offering clinical genetic tests in the form of susceptibility or pre-dispositional tests often called risk assessment tests directly to consumers rather than through more traditional means. And examples of these tests have previously been discussed today, but risk of future development of cancer, rheumatoid arthritis, heart disease, diabetes, and so on.

DR. NETTO: If I may?

DR. WATERSON: Sure.

DR. NETTO: Yes. I think specifically for this category, and as we discussed before in the vacuum of any clinical history, any additional risk factors for several of these, for example bladder cancer, lung cancer, I think it becomes very dangerous to get a false reassurance that you do not have a risk, first, I mean beside the knowledge and how encompassing the tests the seller is offering.

You have to take it in consideration, also, there's advertising

and marketing that even in the companies that we think are requesting regulating, they put it on their website. So in that setting, to come with a negative result is going to be very reassuring for that patient, especially when you don't know anything about environmental risk factors and familial risk factors a patient has and potentially we can do harm by negative as much as we're doing by positives.

DR. D'AGOSTINO: D'Agostino.

To call attention to the Panel, the Panel's attention, that a number of these conditions you can already go to the web, get the Framingham assessment, the Mitch Gail. And also Mitch Gail's not an all seasonal low because he controls for age. They'd be pretty high if he didn't do that. But I think the comments that were just made is that I don't have the comfort that when they do the genetic testing, they're really building in those other variables, and so the sort of response I would have is, hedging at that, what I understand by most of these genetic testing, and I did do a fair amount of looking on the web and so forth, they just go for the gene and let you know that. Built in with the other -- data and so forth, they could be very informative, and it's that mix right now, I think, that they may be dangerous and give you false assurance.

DR. NETTO: George Netto again.

And as a follow-up, I think the problem is that, like we discussed, the harm studies that are looking at anxiety and a couple of other

things, nobody's looking at the harm of missing and how it's affecting the behavior, how much that patient, you tell him you have no risk for prostate cancer, bladder cancer; in years it's going to affect the likelihood that he's going to -- he or she is going to be discovered with advanced disease, so until we get this data, I think it's extremely dangerous.

DR. GALLAGHER: Colleen Gallagher.

I think for myself, I think that some of those dangers might be a little bit mitigated by some regulation that would discuss how that information would be disclosed as well as, you know, what would have to be included in order to release that data to the patient. So I would not be as uncomfortable with making that direct to consumer in comparison to the other two items discussed earlier.

DR. D'AGOSTINO: Can I just -- that's what I was trying to say is that we know we can do very well with some of these conditions, and as long as the genetic testing builds that in, there's a possibility.

DR. HIRSCHHORN: I ask for information. How would you make certain that the age-related -- that the person, the direct to consumer test would be reported to someone who would treat age-related macular degeneration?

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman.

I would like to put a little bit different context on this. Coming

from the point of view that was stated earlier today that a patient has the right to know and, therefore, these should be opened directly to the consumer who wants to know. I don't think any of us are saying that the patient or the consumer doesn't have a right to know.

I would suggest, also, that those consumers who, in fact, are in these small portions of the population who actually go to DTC testing companies would also be good advocates for themselves or their families within the health system, as well, and putting this into the context, do we believe that this is ready to go from the traditional setting of testing processes like everything as simple as anemia or uric acid level into the very complex area of risk assessment, my answer would be, given all of those factors, I would suggest that we are not ready yet to put this directly into the consumers' hands.

DR. WYNE: Kittie Wyne.

I'd like to extend something that Dr. Netto has been kind of getting to but not quite gotten there, which is as it was just said, we have this data about short-term harm, but we don't have any data about long-term benefit and, you know, we teach the medical students that epidemiology can show associations but it cannot show cause and effect.

And so we have these genetic variations that are associated with risk, but what's our data that if we identify, these that we can take an intervention and prevent the disease? What's the long-term data of doing

these kind of studies? And I think that's kind of one of the concerns is, we don't actually know the value of this information.

We need to find a way to apply the information, and right now, we're just letting people go get it, and then they can play around with their own genome and, you know, but we don't know what to do with it and we don't -- do we have any ongoing studies of the long-term benefit of doing these type of screens?

DR. HIRSCHHORN: You mean for age related macular degeneration?

DR. WATERSON: Dr. D'Agostino.

DR. D'AGOSTINO: I have not an answer, but a response to both. Right now, someone can go, in fact, on the Framingham webpage and get their cardiovascular risk assessment, and it could turn out to be greater than 20 percent, which the guidelines say you should be treating, but how do we know they'll go for treatment? We don't really know and that is a danger.

The other thing is that a lot of the risk functions that have been developed at Framingham, as an example, but other places, they would develop on epidemiological data and then there were clinical trials to show, in fact, that lowering blood pressure made a difference, that lowering lipids made a difference and so forth. And I think you raised a phenomenally good question, how do we know this is going to have a long-term effect, a long-term benefit.

DR. WATERSON: Try to get a sense, do we think that this is ready for prime time yet, and then should it go to direct-to-consumer or should it still go through the traditional healthcare channel?

Steven.

DR. LIPKIN: Actually, I was going to say that -- I'm just looking, at least, the examples listed here, and maybe I'm slightly missing the point, but I want to break this down into two subdivisions, okay.

So the first is sort of -- and maybe one of the categories is just not even on the table, but I just want to clarify this. So, you know, in terms of like risk, there are variants, you know, that affect -- they're talking about ear wax and eye color and height and whether you -- and sperm banks, actually. Apparently there are things you can look at to see if you look like George Clooney or things like this that really aren't, you know -- aren't really observed in the medical sphere. And for those, I personally don't see any issue with having these direct to consumer.

But what we've heard today is a bunch of panels that include variants that are in that realm and at the same time, then, also in this other category. So is the -- we're talking in terms of the more cosmetic or you know, non-medical, those are just not even on the table, or are those mixed in because the tests that are being done with, for instance, these -- studies include both.

DR. MANSFIELD: Right. So, in general, we would not consider

tests for the consistency of your ear wax or your resemblance to George Clooney to be medical devices, so those do not need to be included in this discussion.

DR. TSONGALIS: Yeah. So the only issue I have with that is that, you know, we heard a lot this morning about the association studies and so whereas your gene -- constituency of your ear wax may not be clinically important, what happens if it's linked to one of these other markers in that region that's associated with some other disease? And so I think if you're going to do this, all of these potential genetic variants can become clinical tests.

DR. MANSFIELD: Yes, that's -- let me clarify. That is true that usually these would not be considered clinical tests at this time, given that they are not being offered for clinical purposes.

DR. NETTO: I think that only one thing -- and thank you for helping me get there, but the only one thing that I also failed to mention is, is with the ROC curve being so not impressive for these and with the other issues, that's why I keep harping on the negative false, you know, reassurance impression because you're potentially missing a lot in addition to --

DR. LIPKIN: Could I comment? One way perhaps to conceptualize this, too, is the thinking and maybe this is a little hard because there's such a tremendous heterogeneity and variety of diseases, but thinking in terms of absolute risk or having kind of like, sort of like, cutoffs.

So, you know, for -- and unfortunately, each disease would probably be a little different, but you know -- and that's really my experience is that that's what patients really focus on. They're not really interested that their risk is 2.1 times the general population, you know, for colon cancer. They want to know, you know, is my risk 5 percent, 10 percent, or you know, 70 percent. That's what they really want to know.

So for, you know, for things that are below, you know, sort of like 5 percent, and this is something that, I guess, the Agency or in consultation would have to think about what they would -- use these cutoffs. That would sort of fall under, once again, sort of like not really medically significant.

You know, but then there's the potential, I guess, for -- you know, some of these issues with combining these and trying to add them, which also adds the error bars actually, too, in the range of uncertainty.

So I'm just sort of asking, is it possible to consider kind of like having a threshold effect for in deciding what is considered medically, you know, significant and what's not and then not worrying so much about regulating what's not significant?

DR. MANSFIELD: I believe we are searching for answers related to the intended use and not to the clinical significance. So if the clinical significance is low but the intended use is of medical interest, then that is still

in our consideration.

DR. WATERSON: Dr. Hirschhorn, you had a question?

DR. HIRSCHHORN: I'm a little confused. I'm looking for help here.

I thought that maturity onset related macular degeneration required therapy as fast as you could get it and that though it was not -- this is not my area of expertise or anything, that there are not just one single -- there's one single gene that is responsible for much of it, but that there are others now that are appearing, also, so that it's -- in other words, I think it's an area where things are not that clear, and I would like that, therefore, to go -- and I would use that as a criteria for when I would like it to not be -- I would like it to go to a professional before them being passed on.

And I think anything where it's, you know, given and known, et cetera, that's fine, but I think that someone has to go looking down through this series of disorders and ask for that. Like, for example, to my knowledge, rheumatoid arthritis, we don't know what causes rheumatoid arthritis. It's a diagnosis you can make by looking at a patient and as well as a gene, and the therapy is given, so you want to send it off and see whether you may have a gene for rheumatoid arthritis, be my guest.

And I think I'd like it to go, someone to go through all of those disorders that you have here or would look at -- because I think that these disorders lie at the break between those which you really want to go to a

professional and those which yes, if someone wants to do a direct-to-consumer, it would be fine, too.

DR. WATERSON: Okay. Ms. House.

MS. HOUSE: That actually kind of worked really well with what I was thinking where, as a patient, I don't want it to be black and white where across the board we're going to say this you can, this you can't. I think it really depends on the condition and the test and the validity of the test.

And if, you know, the information is described about the patients and, again, I know I keep coming back to that, but I think that, from what we've heard, right or wrong, the patients that are seeking out these tests, you know, want the information and believe that they can understand it, and maybe they'll get some of it wrong, but maybe they'll get something useful out of it.

And the better it's explained and the more clearly it's written out, then I think the more useful the information will be to them, and at the end of the day, it's their information and they should have the right to learn about it. I mean, I don't think they can wait to have all of the answers because I don't think we ever will have all the answers. So if we wait too long, then a lot of misinformation is going to happen.

DR. TSONGALIS: So I suffer from amplification of the optimism gene and complete deletion of the shyness gene.

(Laughter.)

DR. TSONGALIS: But I think, you know, is any of this ready for prime time right now? Maybe not, but I think if it's structured correctly with the help of the FDA and whoever else needs to be involved, that what we're talking about can have a huge, huge impact on healthcare across the board. And so I think we have to be careful of what's really ready for today versus what could be ready in the next short term.

DR. LIPKIN: It seems to me like the -- I'll be very quick. Seems like the discussion, it sort of sounds like we're talking about outlawing these tests, which is not what's on the table. You know, it's not that these are, you know, cannot be provided. The issue is just whether it should be done under a more supervised, you know, medical umbrella or whether it should be offered just without the sort of restrictions, direct to consumers. So these things will be available, are available, and will continue to be available as long as people are interested.

DR. MAHOWALD: The only limitation, of course, to their availability is their cost.

DR. WATERSON: We don't do that.

DR. MAHOWALD: And that's a severe limitation to many people.

DR. WATERSON: We don't -- we're not concerned --

DR. MANSFIELD: Just for your information, we cannot consider cost of the test in our deliberation.

DR. MAHOWALD: No, I realize that. Yeah. It was -- I was thinking of Nancy's point at the end of her talk.

DR. HERSCH: It's still part of the risk/benefit equation, which we are talking about. Even the exact figure may not be, but -- that there's one -- there are avenues where things are accepted into medical practice and are paid for by insurance and then another avenue where they're not, and that changes things a lot.

DR. WATERSON: Go ahead.

DR. HEJAZI: I guess I have a question. By saying that these tests cannot be provided through DTC, are we saying that they're not safe that way, that's why they have to go through a clinician?

And I think I also want to point out that a large majority of people in this country are not under the care of physician, so this is an additional step. The data is available out there, the information is available, but we're saying no, you can't have it unless you see a healthcare provider because it's not safe for you to have it. And I just want to make sure that we all understand that point.

DR. D'AGOSTINO: I thought we're possibly saying that in this present form, they may be misleading and so forth, but they can, like the cardiovascular profiles, can be made more informative by incorporation of other, the appropriate variables and so forth. Now, there's a question after that, do you want it out, but, again, a lot of these cardiovascular/cancer

instruments already exist that don't have the genetics in it, can't do average genetics and make that available.

DR. MANSFIELD: So if I may provide a directing moment, I think we're looking for the weight of risk versus benefits and not whether they're safe. So do the risks outweigh the benefits as directed, consumer test or not?

DR. MORIDANI: I only wanted to mention and comment regarding that the majority of people in this country are not -- and this is just a comment for the record -- that they are not under supervision of a physician because they cannot afford it, so how they can afford DTC, so that also is an issue to remind the Panel.

DR. WATERSON: Okay, one last comment.

DR. SHAMBUREK: You know, I think the way a lot of people are just forming their answers are, I think we're in the pre-personalized era. I don't think we want to be in the personalized era, and we want people to get the information, and we are looking at the risk/benefit, and with this, we heard a lot of comments and people where the prevalence or the incidence, however relative or absolute, it's so low right now, we don't know enough of how to categorize that, and we may, even with good analytical techniques, be giving misinformation. With time, it potentially has the strength of taking us into the personalized where direct-to-consumer, I think, would then, can make their choices. But I'm not sure, with the information that we really have yet, in the pre-personalized era, they can make that choice, where

there's the information that's valid.

DR. WATERSON: Okay. I think I'd like to end that with that comment, too.

DR. MANSFIELD: Okay.

DR. WATERSON: I think that's sort of the general feeling of the Panel.

DR. MANSFIELD: So now please consider the next category of tests, which we have called pharmacogenetic tests. And these are tests that, in general, predict drug response, whether it is a specific drug, a class of drug or not. And some examples are genetic tests that predict response to warfarin, Abacavir, clopidogrel, and so on. Should those -- does the risk of offering them directly to consumers outweigh the benefit or the other way around?

DR. LIPKIN: I have a question. You know, my -- I asked you about FDA policy as to the kits, so I'm a little confused because I believe that the United States, there are direct-to-consumer hepatitis C and HIV kits, which are FDA approved. Is that correct?

DR. MANSFIELD: Those are called over-the-counter, and tomorrow there will be a presentation. They operate a little bit differently than direct-to-consumer.

DR. LIPKIN: I see. So over-the-counter is different from direct-to-consumer.

DR. MANSFIELD: Yes.

DR. LIPKIN: I can appreciate that.

DR. NETTO: But this is treatment, right, not diagnostics?

DR. LIPKIN: Well, this is listed, you know, hep C was listed.

DR. NETTO: Hep C virus treatment.

DR. MANSFIELD: No, it's testing.

DR. LIPKIN: No kits.

DR. MANSFIELD: It's testing.

DR. NETTO: Testing for treatment response, treatment response. These are pharmacogenomic, so it's not to show somebody you have it -- or not. Somebody who is going to be treated for hepatitis C, I do not understand the logic behind me seeking a DTC test if I'm going to be treated with fluorouracil, without even a physician.

I mean, what's the point if -- definitely, you're going to have a physician involved, so what's the value? We keep harping back to the value, well, the physician's going to refuse to do this test. If the physician who was treating you for hepatitis C or for heart attack is not seeing the value in doing this test, maybe there is a rationale and then there is a risk for false information.

DR. WYNE: Kittie Wyne.

The other part of the concern there is the patient will do the test, misunderstand the result, and stop a medication, for example,

clopidogrel, and then come in that night with an acute MI because they've clotted off their stent. So there can be an immediate detrimental effect from stopping their medication because of the way they read the result of the test.

I also can see that patients would get this test and say see, this means I don't need to take this medication whereas they may actually respond to the medication. The pharmacogenetic testing doesn't necessarily mean you don't take the medication; it may alter your dosing of the medication. And so those are things where a provider who understands the testing needs to be able to utilize it and interpret it appropriately.

DR. MORIDANI: This is one of the area that actually I have a favorable -- that I like DTC. One reason is that many physicians are truly resistant to use these type of tests and especially for drugs that the labels are changed for FDA and/or for the drugs that a genetic test is linked to the efficacy of the drugs like tamoxifen or clopidogrel, rather than for toxicity because other biomarkers can be used to monitor the toxicity. And just, that's my input.

DR. HERSCH: But I think that's a choice that could be made clinically, so for -- this is Steve Hersch, sorry.

So, for example, if the test is a test that predicts a higher blood level and so you get side effects at a lower dose, do you do the test or do you see the side effect? It depends on the side effect. So it's a clinical judgment, whether you'll get more value out of a genetic test to predict a response or if

it's a condition where you're going to titrate a medication anyway, then you're just going to do it anyway and the genetic test isn't informative.

So I think there's clinical -- basically, it's a lot of clinical judgment that should and can be involved in the decisions about when and how to use these and how to interpret them.

DR. SHAMBUREK: And of all the examples we see, they're prescription drugs, and I just would be very worried if a patient took it and I didn't know what they were giving them, and perhaps give another drug with another interaction. If it was an over-the-counter drug or something, a direct-to-consumer could be possibly considered, they're making the informed -- the decision on that. However, with these, the physician is controlling and it could be a big risk. The patient, themselves, don't know what is happening.

DR. MORIDANI: Well, one thing is that -- I apologize. I should have got permission. Can I? Yeah. One problem in the pharmacotherapy is access and compliance, so regardless of, you know, whether a genetic test is available or not, still, patients might have a problem in continuing their medications or not. So I truly think that this might be one area that actually help genetic testing to be taking off and incorporated as part of -- as long as individual patients are not targeted for marketing. It's just general public marketing, not, you know, marketing goes with the test.

DR. WATERSON: Joann.

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DR. BOUGHMAN: Joann Boughman.

Could I get clarification from the FDA about the labeling process with the drugs themselves regarding pharmacogenetic tests? It seems like we're separating these two completely, and I know there are some guidelines or whatever that any -- the drugs that are on the market that have pharmacogenetic tests that go with them, whether they should/they can/will/shall be done.

DR. MANSFIELD: The majority of the pharmacogenetic tests are described in the label but not necessarily required. There are small numbers, such as tests for hypersensitivity to Abacavir, and I can't remember about the carbamazepine, that might be a requirement now, but most of them are recommended and not required. But the information is in the drug label, nonetheless.

DR. NETTO: Yeah, but you would hope that the label or the physician's practice is based on -- evidence based. And for us to assume that by providing it direct to consumer, we're trying to build the data this way, that this should be coupled, I think that's not the way medicine is practiced now.

DR. WATERSON: Did you have -- Ralph.

DR. D'AGOSTINO: In the work I do in cardiovascular, clinical trials and so forth, this is sort of one of the most exciting areas. I always think of it with a heavy dose of physician oversight, I mean, does anybody have a

sense, do people actually go out and get these tests on their own and -- I think they should have physician oversight, but I'm wondering do people actually use these tests? Like I see the others -- people, you know, sort of buying the kits and what have you, but this one is hard for me to --

UNIDENTIFIED SPEAKER: The warfarin is used.

DR. D'AGOSTINO: No, they're all used, but they're used, you know -- in my experience, with a very heavy dose of physician oversight.

DR. WATERSON: Okay.

DR. GUTIERREZ: They're usually offered as part of the panel, and by companies like 23andMe has some of those.

DR. WATERSON: Okay. I'm getting the Panel's sense, again, that we feel that this probably still, for the time being, should be under physician or healthcare provider purview.

DR. MANSFIELD: We're ready to move to the last category of nutrigenetic tests. These are tests that estimate a person's responsiveness to a particular food or diet, and examples of this may be recommendations for how a particular food affects your metabolism, your general health status, or your risk of disease. Again, the risk of offering this directly to consumer versus the benefits of doing so.

DR. WATERSON: To say that no tests were really listed in the appendix that related to that, I'm not really sure exactly what kinds of things we're talking about here.

DR. MAHOWALD: Unless I knew more about these particular tests, this looks to me, in comparison with the other categories, as least problematic, the closest to replicating the notion of medical products or strategies that are sold that are really not clearly directly related to health.

I mean, the difference between things that patients can get that are necessary to their health and things that they get from medicine that are not necessary to their health, you know, some examples of cosmetic surgery, for example, is closest to this category, in my view.

DR. WATERSON: Are there any tests that recommend that you take a lot of vitamin B<sub>6</sub> or something like that, that might be toxic or something like that?

DR. GALLAGHER: I don't know of any particular tests, but I know that there are a number of people who are involved in complementary and alternative forms of medicine who will often do blood tests and then make recommendations about what foods you should eat and whatever based on your blood type, things like that.

And many of those people are physicians, many of them are not. And so I think, just to be aware that there are people who are involved in complementary medicine as practitioners, as well -- in terms of being medical providers as well as consumers, if you will use that word or customers, using their services who certainly are very interested in this type of possible genetic testing. So what you're asking, saying you don't know -- I

just know that that's a big portion of what they're beginning to develop.

DR. GREGG: Yeah, this is Jeff Gregg.

I think, for example, they might be discussing MTHFR, and that would be something that could be good or could be bad. For example, women that are homozygous TTs may require more full light and that there's blogs and things on the Internet that suggest, you know, very excessive amounts of full light. The new literature coming out with fortification of -- that it may actually be carcinogenic. So there are some issues here where some of this information could be harmful.

DR. HIRSCHHORN: May I? Yes, although everyone knows about it, I guess, but lactose intolerance, if you go to your supermarket, there's all things to use for lactose intolerance, but the mutation, you could make the diagnosis by DNA observation, and it does have an ethnic change so that the mutation is different in African-Americans and whites. And maybe it would -- it might be very useful because I know that my grandchildren, the pediatrician refused to consider that they might be lactose intolerant, and it's not uncommon. And it's a tremendous help, but I think there are easier ways to do it.

DR. SHAMBUREK: Bob Shamburek.

I think one of the problems is, you know, I think lactose intolerant wouldn't fall under this -- I mean, I think that's a medical condition as opposed to a food interaction. I think we don't know for sure, but I think

in this case, the level of anxiety, the potential risk, is very low compared to the other tests, but I also think, and maybe the FDA people could let us know is will they still fall under the purview that it has to be analytical, it has to be validated, and although if that's true and they could come out, perhaps a level of risk is lower that it could be a direct-to-consumer.

But I think we see so many non-validated studies, and I think without good examples, I'm not sure how I can say, but I think the level to the patient right now is low, but something like lactose intolerance, I wouldn't -- I would think would fall under another category.

DR. HIRSCHHORN: There are many ways to skin that one, so I'll go with whatever you want.

DR. WATERSON: Okay, it's -- one more.

DR. WYNE: Let me just try to add one perspective to it. We've been talking about tests that we have, we think, known diseases associated with them or known conditions or something, and now we're talking about tests that have claims related to how status or risk of disease and are currently being used in a medicalized situation, and the patients are perceiving it as an FDA-approved medical test.

I have patients who come in and bring me their reports from their other doctor, and they think these are medical tests that are testing their risk of disease, and so they're following that person's advice and buying 25 supplements from that office to address these risks. So I think the issue is

that these tests need to be evidence-based in some way.

But also, I think the concern is the companies testing them, if there's no regulation of the quality of their testing, what are they actually testing and what are they doing with the samples that they're acquiring? So I would just worry about what's actually being told to the person. There are dangers in excess amounts of some vitamins, so it's not without some risk.

DR. WATERSON: Tiffany.

DR. MANSFIELD: So, again, clarifying the assumption should be that FDA would be regulating these and assuring the analytical and clinical validity.

MS. HOUSE: I mean, that kind of goes to what I was going to say in that as long as there is something to what these tests are saying, if -- know that it's verified, then I don't know if I see harm in recommending a certain diet if the testing is there.

I mean, I don't know if it's that different than going to the bookstore and there's, you know, millions of different diets. That's not being regulated, and people are going to do that, so at least this would be better, if you have the validity behind it.

DR. WATERSON: Dr. Lubin.

DR. LUBIN: So in terms of testing, nutrigenomic testing, to identify the propensity to metabolize or not metabolize certain nutrients where recommendations might result that you may need more folic acid, you

know, that's one issue, but sometimes we see these tests being marketed as to improve your heart health or boost your immune system or other claims that are made, so this comes back to the issue of really being able to look at the claims and seeing whether there's evidence to support those claims, and I think that's where we need to draw the line.

DR. WATERSON: Okay.

DR. TSONGALIS: Just one question. Does the FDA regulate vitamin D testing?

DR. MANSFIELD: Vitamin D testing is a medical device. Many vitamin D tests are offered as laboratory developed tests and are thus offered under enforcement discretion. However, they are under FDA's statutory authority.

DR. WATERSON: Okay. I don't know if I'm getting a clear sense from this particular one, but it looks to me like, I think, primarily the concerns were the claims that are made for the testing and not so much for the testing, itself.

DR. MANSFIELD: Thank you. I believe we're going to skip the second question here because I think you've sort of answered it with your discussion, but I need to read it, anyway, so I'm going to read it and then move on to the next question: Should any of the categories or specific genetic tests listed below, or other genetic tests or categories, be offered solely on prescription?

So the next question: Please discuss, for those tests that you believe the benefit outweighs the risk for being offered directly to consumers, are there results for certain genetic tests, that even though the patient can order the test and send in the sample, the results should be routed through a clinician, a healthcare specialist, even if the test is offered directly to the consumer?

And you may go through the categories at random, if you like, or you may go through them one by one.

DR. WATERSON: Why don't we start at the top and go through the carrier tests? It seemed to me that we felt that those should all be routed through a physician or a healthcare provider that is trained to give those results.

DR. MANSFIELD: Please specify if you think they should only be ordered by a provider or whether a patient may order them and have the result routed through a clinician.

DR. WATERSON: I think from our prior discussion, I thought we came to the conclusion that we still think this should be ordered by the provider. Pardon? Does anybody else have any input for that?

DR. TSONGALIS: So I have to disagree. You know, I think that if this is structured differently than what we have now, that it can be ordered by a consumer as long as results get reviewed by a provider.

DR. MAHOWALD: Yeah, I feel there are certain diseases or

certain categories in which it would be acceptable, also, to not have the clinician order.

DR. WATERSON: Okay, we're talking about categories. We're trying to make a blanket statement here about all --

DR. SHAMBUREK: Yeah.

DR. WATERSON: I don't think we're -- are we ready for all? We're certainly not ready for all, but we may be ready for some.

DR. SHAMBUREK: Right. But I'm not even sure we know yet which --

DR. WATERSON: Which is --

DR. SHAMBUREK: Which could be. I think there could be a time, but I don't think yet we know that.

DR. HEJAZI: And I think there is a distinction between saying that there will be better clinical utility or to be advantage of routing it through a healthcare provider versus saying it is -- we do not allow it to be direct to consumer because it's not safe, so again, I want to go back into that point.

DR. WATERSON: Tiff, did you --

MS. HOUSE: I was going to agree, that I think that there are probably cases where it would be fine to go directly to consumer. I think that it would need to be a more in-depth case-by-case determination that we're not making here.

DR. SHAMBUREK: I just wonder if someone could describe what routing through a physician is, what is that process? I mean, is that a mandatory one? Does it -- do they, the patient or the consumer order it and they pick it up from their physician? So I'm trying to figure out what routing through a physician is.

DR. MANSFIELD: I believe that that is correct, that the test result would be -- our ideal was the test result would be reported to the physician only and the physician would pass the results on to the person who ordered it.

DR. SHAMBUREK: Then I wonder whether or not the physician should decide on the 28 versus 8-variant cystic fibrosis. I think the physician should then have an input or they may decide, once they get the 8 cystic fibrosis, they now want the 28 and it will cost whatever amount more.

DR. LIPKIN: I'd be concerned about a race to the bottom, you know, if you offer CF testing and someone looks and sees \$100 versus \$500 and they don't know the difference, that the \$500 test is ten times, you know, more extensive, that's a problem.

DR. NG: I'm sorry, Valerie Ng.

I think the cat's out of the bag and this is what I want, carved out with a physician in the middle. I want any result that has a high predictor that that person's going to develop disease, filtered through a physician so that physician can get -- I'm sorry, another qualification, that you can actually

do something about it and prevent that disease or ameliorate the symptoms. I want that funneled through a physician.

DR. MORIDANI: I also feel the same way, that some of these tests could be offered to a DTC but, you know, to -- filtered through the physicians because, you know -- validity and I don't think the relativity of some of these tests are well known.

DR. WATERSON: Tiff.

MS. HOUSE: Is it really a concern that a patient is going to get information that says you have this, you have a high risk for this, whatever it is, and they're not going to share it? I mean, I know that some of the results from these studies said one thing but they were very short term follow-up, I mean, within a year, if the studies had been prolonged.

I personally, as a patient, if I got a test result like that, I'd take it to my doctor. So I don't know if that's a concern. I think that it would actually be the opposite. I think they would probably run to their doctor with this information.

DR. NETTO: I think the doctors are always going to be in the interpretation even of the negative testing, and we can't assume that all the consumers are going to have enough sophistication to understand the genetic test results. We just finished saying several of us, even us trained physicians, are not as well trained with this, so I think it's a lot of burden to put on the consumer. So in my opinion, at least the physician needs to be involved in

communicating the results.

DR. GALLAGHER: One of my concerns is that, you know, for unscrupulous companies, and there are some, that they might try to do something where they hire a physician who they would route it through to give to, directly back to the consumer.

And I say that I'm concerned about that, using a very simple example, I mean, how many times on the Internet in your e-mail do you find the spam from some company selling Viagra or some other drug that, you know, requires a prescription that, you know, there's a doctor at the other end who's going to sign the prescription so you can get it over the Internet. So I think we have to be really careful about the idea of routing through a physician and how that would occur, so that would have to be regulated, how that would occur.

DR. NG: What I'm hearing around this table is kind of really ironic because it's, to me, everybody's struggling with systems that are already in place in accredited laboratories. The issue about somebody who has a result that predicts a high rate of penetrance and bad disease is a critical result, right? We know how to communicate critical results if you're an accredited lab. If you're not accredited, you don't even know what to start with.

Tiffany, in response to your comment, the studies we heard today, you know, 99 percent of the people got the results, never followed up,

never shared it with their docs. But that has to be qualified with the odds ratio of those results was very low, i.e., meaningless, so who really cares. In that sense, I don't think we're doing any harm, in which case I don't care if a consumer gets it. If a consumer gets it and it's meaningful and I could've done something about it, I'd feel really bad if I didn't do that.

DR. LUBIN: So assuming that this area will grow in some direction, another question to ask is, was the obligation and potential burden on the physician who was presented with the result of a test in which they did not initiate but may have an impact on the care of the patient or may delay care that wants to be given but because of this test, there are other actions that need to be given, to be taken.

DR. WATERSON: Okay.

DR. LEE: I guess I'm just a little confused. If we sort of agreed that most of these tests required physician oversight, genetic counseling, then I don't see why the information should be routed directly to the patient. I mean, it should still go through the healthcare provider, so I guess I'm confused why we're discussing this.

DR. MANSFIELD: Among those genetic testing, direct-to-genetic, direct-to-consumer genetic testing -- it's getting late -- tests that were discussed, we would like to know if your opinion would change about prescription use and so on if the results were, in fact, routed through a physician rather than given directly to the consumer. We do have examples

of this currently in which over-the-counter tests, the patient may order the test, take the test, or send the test in to the lab, and the result goes back to a physician who then calls the patient.

DR. HIRSCHHORN: I just wanted to say that it's standard if your physician gets tests you are entitled to, and it's routine if you tell your physician that's what you want, that every test that comes through also goes to you, so -- and this is particularly for Tiffany. That should be standard procedure, and it is, to my experience.

DR. DAVIS: Margaret Davis.

I just thought -- and listening to you, of course I'm not in the industry, but as a consumer, the physician oversight would be just another example of the check and balance on making sure that the test scores are not misinterpreted or misleading causing the consumer, who used it, to go in a direction that's contrary to their best interest, so I see it as a check and a balance on making sure that these tests are interpreted correctly.

DR. WATERSON: One more. Bob.

DR. SHAMBUREK: One very small point. The term is "a physician" or "your physician." So "a physician" can be a company physician, and I think that's an important point.

DR. WATERSON: Okay, I think I'm getting the sense that it is, if there were situations in which persons could order the tests on their own, that we would like the results to go back through a physician or a healthcare

provider that's trained to interpret the tests. Do you think we need to consider each category separately, or is there any discussion that any of these other categories would be any different than the first category?

DR. MANSFIELD: Unless there are comments within the categories, there is no need to go specifically through them.

DR. WATERSON: Okay.

DR. MANSFIELD: Okay, so that is Part (a) of Question 1.

Part (b) of Question 1: Please consider that clinically significant results are required to demonstrate safety and effectiveness of medical devices. Should personal utility, as described earlier today, be incorporated in consideration of clinically significant results?

DR. WATERSON: Which letter is that?

UNIDENTIFIED SPEAKER: That's (b).

DR. WATERSON: Oh, (b). Okay. Thank you.

DR. GALLAGHER: Could I ask for an explanation of what you mean by personal utility?

DR. MANSFIELD: Yes, I will try to clarify that consumer groups, genetic testing companies, and others have indicated that people who buy direct-to-consumer tests may find personal utility in knowing whether they are at risk or not at risk for diseases or whether they carry a mutation or not carry a mutation. Should we consider that at FDA in our deliberations on clinically significant results?

DR. WATERSON: Do you have the statutory authority to do that?

DR. MANSFIELD: Assume that we do.

DR. WATERSON: Okay. Mary.

DR. MAHOWALD: Could you explain more fully what is meant by clinical effectiveness? It's only the word "effectiveness" here, but to the extent that a test result may be incredibly ambiguous because of the absence of other factors that are fed in to the risk assessment, it's hard for me to understand what is meant by clinical effectiveness. How would you determine that?

DR. MANSFIELD: Alberto is looking for the statutory definition of effectiveness, which I think is the best way to understand it. I will paraphrase it now, as long as you understand that this is a paraphrase, that effectiveness means that a test result is clinically significant in the target population. That means it has some clinical meaning or bearing on the patient or person.

DR. MAHOWALD: And there's no mention of how significant. It may be, you know, significant in a miniscule way --

DR. MANSFIELD: Right.

DR. MAHOWALD: -- which belies the term "significant."

DR. MANSFIELD: Yes, we're not weighing the degree of significance. It's that does personal utility weigh in to clinical significance.

DR. RANSOHOFF: Does clinical significance mean outcome, or does it just mean I changed my behavior or the way I look at things? Does it mean something objectively got better?

DR. MANSFIELD: No, not necessarily. Not unless that is your claim.

DR. LUBIN: There have been instances where many of these, I think, DTC tests have been marketed with the claim of personal utility in the disclaimer that these tests are not being offered for a clinical purpose. I think there is no way to ensure or to measure how that product will be used by the customer, and there are tests, whether you're talking the RCA, Huntington's, or what have you, in which results may be inferred or even stated in terms of the results returned to the client that do have clinical meaning.

And, therefore, unless personal utility can somehow be separated from clinical effectiveness, then I think that it's very difficult to just having it as an out that any test can be offered as long as you say that it's only being offered as one for personal utility and discounting, you know, when there is also clinically relevant information being provided.

DR. MANSFIELD: I would like to read the statutory definition of effectiveness. This is found at 21 C.F.R. 860.7(e)(1) for the record. "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant proportion of the target population, the use of the device, for its intended uses and conditions

of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

DR. NETTO: I don't think, from we heard this morning, there is any data to prove that it has been proven clinically significant, effective in that information.

DR. SHAMBUREK: The only analogy I'm seeing is, is if a patient wanted personal utility to be on an antibiotic and they don't have a clinically significant infection, we wouldn't give it. If a patient wanted a PET scan to rule out cancer and they were young, we wouldn't do it. But perhaps if a person came in and said I'm adopted, I would like to know if I have cystic fibrosis or I'm a carrier and there's a reliable test, there would be a clinical significant result, which I think the information, per se, with counseling and a reliable test, wouldn't do harm as it might in the two other cases.

DR. RANSOHOFF: Just to follow up on Dr. Shamburek's example here, if a patient took an antibiotic that we knew wasn't going to work but afterward said I took it, I got better, and I've got a lot of personal utility, how would we judge that? And I think what I would put on your radar screen is that while personal, how people feel about things, genuinely is important and it's easy to imagine how certain kinds of tests could resolve serious things and make people feel better, I think it's also very susceptible to marketing and manipulation like selling cigarettes or automobiles or other things that make people feel good, exactly with the antibiotic.

I think if -- patients will tell you, patients come in all the time with diets or medications that, to me, look like they make no sense at all, but they're really pleased and convinced by them, and I think they might say that that's the kind of personal utility, and if we sort of don't keep that on our radar and try to manage it, it can cause a lot of mischief. And that's the problem with personal utility. There may be a good side, but there's a bad side, too.

DR. D'AGOSTINO: Let me try a statistician's spin on this. I oftentimes get asked what do we mean by clinical effectiveness, and it's usually that we've looked at the data and there's statistically significant results. So in this case, we're getting diagnoses or what have you that's beyond chance fluctuations, and then the clinical significance does that, statistical significance translates into something that's meaningful clinically.

And now, I guess, what we're being asked is something warm and fuzzy, is there a personal touch to it that we can add, and I don't know, if you want to, you can say we should do it, but I don't know on what basis you'd do that.

DR. WATERSON: Okay, are there any other comments? It seems to me that -- Tiffany. I'm sorry.

MS. HOUSE: That's fine. I think that your example was very good about adoption, though, and I think that's more and more cases where maybe a person won't know about their biological parents, in which case

maybe it's not going to be great information that they get, but it's better than they would have without it.

So I think that in some way that is personal utility. Maybe it's not clinically significant as it, you know, somebody that does have their family history, but I don't think you should discount it all the way. I think it, you know, could be considered both for and against and should be considered in that, you know, both the pros and cons of the personal utility.

DR. WATERSON: Mary.

DR. MAHOWALD: I just want to suggest that placebos are shown to be clinically effective.

DR. GALLAGHER: I just want to say that I think that personal utility is a very distinctly different thing from clinically significant results, and so I probably would not include it in the definition.

DR. WATERSON: I would agree. I think that's the sense I'm getting from the committee as well.

DR. MANSFIELD: And the final part of Question 1 is Part (c): There may be a proportion of test users who express anxiety about reported test results. Should this be considered in assessment of safety and effectiveness? And I would say particularly consider the safety here. Is expression of anxiety a safety issue?

DR. WATERSON: Anybody want to tackle that one?

Colleen.

DR. GALLAGHER: Well, I think that if the assessment of anxiety shows that the anxiety is very high and causes people to take action that is detrimental to them, then I think that it certainly should be. But I think that most of what we saw, at least earlier today, was that the anxiety was not at such a level that that changed the safety factors.

DR. LIPKIN: So we've gone through a discussion and described what's really sort of clinically -- or in the previous discussion the past couple hours, you know, what's really clinically significant and, you know, what are not, maybe less lower on the priority queue.

And now here's another question, you know, about anxiety, so what we've really heard so far and the literature suggests it, I mean, the quantitative effect of anxiety is pretty minimal, so probably I would -- my personal opinion is sure, you can incorporate anxiety, but the data that's out there today suggests that this is really not clinically -- it doesn't meet the criteria for clinical significance that we've been applying, you know, really to the tests, themselves.

DR. WATERSON: My problem with some of those studies, they didn't really include -- the marker didn't include, like, the BRAC 1 testing. It was pretty much more the multi-factorial diseases and not this pre-symptomatic testing.

DR. D'AGOSTINO: They're also based on, you know, 50 percent of -- well, the potential population and so forth, so they -- and the presenters

were aware of that and did illuminate us on it.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman.

I think part of this original question may have come -- and this is projection to a certain degree, obviously -- that the expectation or anticipation of anxiety is part of the paternalism process that we are trying to get rid of in this whole process, that even in the personal utility issue but in the assessment of any safety, if there are legitimate data that indicates anxiety is a risk factor, is a minus in this balance, that that would be different than merely the anticipation or the wonder of wouldn't it be possible that people would be anxious. Those are two very different kinds of things, and we want to be rid of the anticipation of anxiety.

DR. SHAMBUREK: And I think you made the point that the pre-symptomatic is only going to be a fraction or a percentage of population screens, and the safety issue might be in those, as we heard with Huntington's chorea, so those are going to be the unknown ones, you're going to see 100 patients and it's not -- so, you know, I think it has to be considered. And I think everyone who presented data said this is preliminary, this is new, we don't know, we're not looking at the overall U.S. population. We're looking at people who are wanting these tests, perhaps, for the information, so I think we have to be a little cautious there and know that there are certain pre-symptomatic, I think, do have anxiety involved with

them.

DR. WATERSON: Are there any other comments?

DR. HERSCH: Just a question. Could the FDA maybe illuminate further what they're looking for in this question?

DR. MANSFIELD: Okay, yes. I'm sorry. We have heard from several speakers today about studies that have been done about anxiety expressed as a result of direct-to-consumer testing. One of our concerns is that is the presence or absence of anxiety a safety factor that we need to consider. And in many cases, I will say not from necessarily the people here, it has been stated that patients are not anxious about these results, therefore, they are safe.

DR. HERSCH: This is Steve Hersch again.

So I would say a lack of anxiety is not very helpful in terms of being an outcome for whether something is safe or not. It's just not -- I don't think it's informative. The presence of anxiety is, you know, similarly is not necessarily reflective of -- it may well be something that comes with a particular test, but it also doesn't -- it's also -- it's like a possible AE, but it's not the main course, when you think about safety and effectiveness, unless there are tests that are being performed specifically because of whether they're predictive of anxiety, then I think anxiety might be more relevant. But where we're talking about things that are in realms that are not specifically around anxiety, it's just it's more kind of something that may travel with but

not really inform whether any questions, I think, about regulation.

DR. RANSOHOFF: Would the Huntington's test be an example of anxiety?

DR. HERSCH: Sure. I mean, there is lots of anxiety associated with the test, with not getting the test, with --

DR. RANSOHOFF: But there would be significant --

DR. HERSCH: -- whatever results you get. So but it's still -- but, you know, it's again, for -- you know, with a test that, to use some of the terminology what we've had before, that falls under high risk, meaning the import of the test is a very high health significance, then naturally anxiety is going to be part of that. When there are tests that have little or uncertain health consequences, then it would be surprising if anxiety was part of that.

DR. RANSOHOFF: So it counts, but it's an issue of degree, it sounds like?

DR. HERSCH: Sure. No, it's just something that you would expect to go with the significance of the test and the significance of the answer for a patient. So, again, it's a covariate, not the main course.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman.

If I understand the FDA review process at all, it seems to me that what we are saying is that anxiety data should not necessarily be a requirement in the review process, but legitimate data about the presence of

anxiety shouldn't be ignored if presented.

DR. WATERSON: Okay, are there any other comments? I think, in my mind, I think what Joann said probably reflects what the committee is trying to say. We're going to go on to Question 2?

DR. MANSFIELD: I believe we'll hold that until tomorrow, if that's okay.

DR. WATERSON: Do you have any other comments?

DR. GUTIERREZ: No, I think we've done well for today, and we probably should start with the other two questions tomorrow.

DR. WATERSON: Okay. All right. The last thing on my little script here is to thank everybody, and I truly do thank everybody for all their useful input, both from the contributed speakers today as well as from the Panel. And we will meet again tomorrow at eight o'clock, and I still think the same proscriptions that were given at lunchtime still hold. We should probably not be talking about any of the discussions outside of the Panel.

Thank you very much. I think the meeting is adjourned for today.

(Whereupon, at 5:30 p.m., the meeting was adjourned, to reconvene the next day, March 9, 2011.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

MOLECULAR AND CLINICAL GENETICS PANEL

March 8, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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