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 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

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March 9, 2011  
 8:00 a.m.

Holiday Inn  
 Gaithersburg, Maryland

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MEETING

(8:00 a.m.)

DR. WATERSON: I would like to call this meeting of the Molecular and Clinical Genetics Panel to order.

I'm Dr. John Waterson, the Chairperson of the Panel. I am a clinical geneticist from Oakland, California. I work at the Children's Hospital at Oakland.

At this meeting, the Committee will discuss and make recommendations on scientific issues concerning direct-to-consumer, DTC, genetic tests 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 with Ms. House.

MS. HOUSE: Tiffany House, Patient Representative.

DR. DAVIS: Margaret Davis, Consumer Representative.

DR. HEJAZI: Shahram Hejazi from BioAdvance, Industry Representative.

DR. MORIDANI: Majid Moridani, Texas Tech, area of expertise, chemistry, toxicology, and DrugNet AAPS.

DR. LIPKIN: Steve Lipkin. I'm a clinical geneticist at Weill Cornell and New York Presbyterian Hospital.

DR. HIRSCHHORN: Dr. Rochelle Hirschhorn, New York University School of Medicine. I am a geneticist and an immunologist.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, statistician and with the Framingham Study.

DR. BOUGHMAN: Joann Boughman, trained as a statistical geneticist and board certified medical geneticist, but as executive vice president of the American Society of Human Genetics, I work primarily in the policy area now.

DR. LUBIN: Ira Lubin, I'm board certified in clinical molecular genetics. I'm Team Lead, Genetics Division at Laboratory Science and Standards, Centers for Disease Control and Prevention.

DR. LEE: Charles Lee, Brigham and Women's Hospital, Harvard Medical School. I'm a board certified clinical cytogeneticist.

MR. SWINK: James Swink, FDA. I'm the Designated Federal Officer.

DR. NETTO: George Netto. I'm an anatomic and clinical pathologist and a molecular pathologist from Johns Hopkins.

DR. NG: Valerie Ng. I'm a board certified clinical pathologist, retired professor from the University of California San Francisco, currently lab director at Alameda County Medical Center.

DR. GREGG: Dr. Jeff Gregg. I'm from the University of California Davis, Department of Laboratory Medicine.

DR. GALLAGHER: Colleen Gallagher, Chief of the Section of Integrated Ethics and MD Anderson Cancer Center, clinical ethicist and associate professor of clinical care and cytotechnology.

DR. TSONGALIS: Greg Tsongalis. I direct molecular pathology at Dartmouth.

DR. HERSCH: Steven Hersch, Professor of Neurology at Massachusetts General Hospital and Harvard Medical School. I do clinical and laboratory research for Huntington's Disease.

DR. MAHOWALD: Mary Mahowald. I'm a professor emeritus at the University of Chicago. I've worked mainly in clinical ethics with a focus on women and genetics issues.

DR. RANSOHOFF: David Ransohoff from the University of North Carolina, an internist and a clinical epidemiologist interested in the evaluation of diagnostic tests and creation of guidelines.

DR. SHAMBUREK: Bob Shamburek. I'm with the Intramural Program. I'm with the National Heart, Lung and Blood at the NIH. My interest is I run the lipid clinic and follow many patients with rare lipid genetic disorders.

DR. WYNE: Kittie Wyne, endocrinologist. I'm the director of diabetes research at the Diabetes Research Center at the Methodist Hospital Research Institute in Houston, Texas.

DR. GUTIERREZ: Alberto Gutierrez. I'm the Director of the

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Office of In Vitro Diagnostics in the FDA.

DR. WATERSON: Thank you very much. If you've not already done so, please sign the attendance sheets that are on the tables by the doors.

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

MR. SWINK: Good morning, everyone. I'll 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.C. 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. The FDA has determined that members and consultants of this Panel are in compliance with 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 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 special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion 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 purpose 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 direct to consumers include:

- (a) Genetic carrier screen for hereditary diseases, for example, the cystic fibrosis carrier screening;
- (b) Genetic tests to predict for future development of disease in currently healthy persons, for example, the test to predict risk of developing breast or ovarian cancer; and
- (c) Genetic tests for treatment response prediction, for example, tests to predict whether an individual will respond to a specific drug.

(2) The risk 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.

(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 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 part of the official transcript.

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 discussions involve any other products or firms not already on the agenda for which a 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 the firms at issue.

For the duration of the Molecular and Clinical Genetics Devices Panel meeting on March 8 and 9, 2011, Ms. Tiffany House, Dr. Steven Hersch, 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 of the Center for 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 was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs on February 28, 2011.

Before I turn the meeting back over to Dr. Waterson, I would like to make a few general announcements

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (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 press are not permitted in the Panel area, which is the area beyond the speaker's podium. The press contact for today's meeting is Erica Jefferson. There she is. 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 sessions today and have not previously provided an electronic copy of your slide presentation to 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. We will now hear the FDA

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presentation. At the conclusion of this presentation, there will be time for questions from the Panel members, and I believe that we will probably take questions after all the speakers have spoken.

At this time, the first FDA speaker is Dr. Reena Philip, Deputy Director, Division of Immunology and Hematology, OIVD. Dr. Philip.

DR. PHILIP: Good morning. I'm going to talk about how FDA evaluates prescription genetic tests. Prescription genetic tests are similar tests as direct-to-consumer genetic tests, except that prescription genetic tests are offered by prescription, whereas DTC genetic tests are marketed directly to consumers, where a consumer can order these tests and receive test results without the involvement of a physician.

This afternoon, the Panel will be discussing the level of evidence that is needed to support clinical direct-to-consumer genetic tests. As a background for this Panel's discussion, my talk explains how FDA evaluates prescription genetic tests IVD devices. That is the valid scientific evidence that FDA evaluates in order to determine that these prescription genetic tests are safe and effective.

According to the device regulations, two types of evidence must be evaluated by FDA for all in vitro diagnostic devices. That is safety and effectiveness.

Safety assessment includes evaluation of reasonable assurance based on valid scientific evidence that the probable benefits to health from

use of the device outweigh any probable risks. Effectiveness assessment evaluates whether there is a reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results.

Safety and effectiveness for IVD devices will generally be determined based on valid scientific evidence, that is, both analytical and clinical validation data. I will explain these in detail in my later slides.

During the last decade, FDA has cleared a number of prescription use clinical diagnostic tests that assist genetic variations. Some are single analyte genetic tests, for example, Taqman-based assays to detect just one mutation; and some are multiplex genetic tests, for example, genotyping arrays or bead-based technologies that can probe multiple variations in the same gene or multiple genes.

These are some examples of a FDA-cleared prescription genetic test. Example, for single analyte genetic test include Factor II, Factor V, NTHFR, nucleic acid genotyping test that are cleared as an aid in diagnosis in patients with suspected thrombophilia. FDA has also cleared some multiple analyte genetic tests such as cystic fibrosis genotyping test, which is cleared for carriers testing, newborn screening, and confirmatory diagnosis. Also direct metabolism tests that shows genotyping for CYP2D6 and CYP2C19. Warfarin sensitivity genotyping test such as CYP2C9 requires even genotyping test.

In addition to these genetic tests, FDA has also experienced reviewing genomic tests that are used to predict risk for future development of disease or recurrence of already diagnosed disease.

With this introduction, I will be focusing the rest of my presentation on: What does FDA review for prescription genetic tests?

FDA pre-market submissions include intended use, device description, pre-analytical, analytical and clinical performance data and labeling. If applicable, the submission also includes instrumentation and software documentation and manufacturing documentation.

In the next couple of slides, I will cover what is typically required for pre-analytical, analytical, and clinical performance demonstration, as these are more pertinent to this audience. I am not going to touch on device description, instrumentation, software and manufacturing in my talk.

For most IVDs, the intended use and indications for use are often folded together under the umbrella of intended use. Intended use is the central concept in FDA regulation. The intended use for an IVD device is determined according to the claims the sponsor intends to make for the device. The intended use specifies what the test measures; that is, what is measured, identified or detected by the test; that is, specific analytes, specific genes, proteins, polymorphisms or signatures. The intended use also specify the clinical indications for which the test is to be used, such as

aid in diagnosis, for carrier testing, for risk assessment, et cetera. The intended use also specified the specific population for which the test is intended to be used, such as carrier testing for at-risk couples planning pregnancy, diagnosis of individuals with particular phenotypes, general screening, et cetera. The intended use should also specify the setting in which the test is meant to be used, such as clinical lab, point of care, over the counter, et cetera.

Here is an example of an intended use of cystic fibrosis DNA test FDA has cleared. As you can see here, the intended use specifies what this test measures; that is, the test measures mutations and variants in the CFDR gene.

The intended use also specifies the clinical indications and the specific populations in which this test is intended to be used; that is, it is intended to be used for carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children. The intended use also specifies the setting in which this test is meant to be used; that is, it says here it's for prescription use only. The intended use also specifies the specimen type and source that the test is cleared for; that is, it states here it's for human blood specimens.

Here are the two points I want to reiterate with regards to the intended use; that is, the intended use for an IVD device has a clinical indication for which the test is intended to be used and the intended use is

determined according to the claims the sponsor intends to make for the device. Depending on the claims made in the intended use, the type of validation studies needed will vary.

Now I will talk about the three critical components in evaluating the performance characteristics of a new prescription genetic test: pre-analytical, analytical and clinical performance of the test.

When FDA evaluates prescription genetic tests, FDA asks enough questions of pre-analytical to support the safe and effective use of the test. FDA evaluates each step in the pre-analytical process, such as sample collection, transport, storage options and nucleic acid extraction that is recommended by the sponsor. This ensures that the test is validated using specimens that are handled in the same manner as is recommended in the test label with respect to collection, storage, shipment and extraction methods.

Another critical component in the evaluation of prescription genetic tests is validation of the analytical performance parameters. Analytical performance evaluation demonstrates whether the test measures the analyte it is supposed to measure, how correctly it measures the analyte, and how reliably it measures the analyte.

These are, in general, the types of analytical validation studies FDA asks for. Analytical performance requirements may vary with the intended use; the technology; quantitative versus qualitative tests; use or

setting, for example, single lab versus multiple labs; how results are reported, whether it's individual analyte versus multiple analytes in nature; and the setting, the labs versus physician. Although all these could be relevant to a prescription genetic test submission, due to the lack of time, in today's talk I will only focus on accuracy and precision.

This is the most commonly used definition of accuracy.

Accuracy is the closeness of agreement between the results of a test and the result of reference method.

In genetic tests, accuracy is demonstrated by comparing the new test results to an appropriate reference method, such as bidirectional DNA sequencing, or to a medically established clinical truth or to a suitable composite comparator. Accuracy studies demonstrate that the new genetic test detects the genotype it claims to detect and it does not detect mutations or polymorphisms when none are present.

Samples used in these studies are patient samples derived from the intended use population in order to show that the test will perform as claimed in a clinical setting. Each of the claimed mutations and variants detected by the test are represented in the samples used in the accuracy study.

For genetic tests, each particular genetic characteristics that are measured by the test is considered as an analyte. For example, in cystic fibrosis testing, each disease-associated nucleotide change that is measured

by a given test is considered as an individual analyte. As part of the analytical performance evaluation, FDA requires accuracy data for all analytes measured by the test to support the test performance, that is, to evaluate that all claims on all variations reported out as accurate. Inference of performance from one analyte to another is not acceptable.

Here is an example of why FDA asks to demonstrate the accuracy of all the analytes measured by the test. You can see from the table here, that when you consider all the analytes together, the percent agreement is 98.4. When each individual analyte is looked at, most of them have a percent agreement of 100 percent, whereas some of them might have as low as 66 percent. So this can be a problem. This is why FDA asks for performance data for each characteristic measured by the test.

Sample sizes for analytical validation are often described in guidance documents; accepted standards, such as CLSI documents; or statistically calculated validation protocols, which are often reviewed during our pre-ID interactions. In general, sufficient validation data will establish the acceptance performance level for each analyte, and for the test overall with a calculated 95 percent confidence interval.

In addition to evaluating the accuracy of the new test, evaluating precision is also very important. Precision studies demonstrate that the intended users can get reliable, reproducible results. Ideally all sources of variability will be identified and assessed.

In general, any variables that changes from day to day or week to week, is examined for its impact on assay precision. Variability in extraction to extraction between instruments, between reagent lots, between days, between runs, between assays, and between operators is assessed. If the assay is not offered from a single lab, then between sites variability is also assessed.

Precision studies test the same panel of samples and cover all claimed mutations or alleles claimed in the intended use. Clinical samples are used in precision studies. If cell lines or plasmids are used for any very rare mutations, then they should be spiked into the matrix to make a natural sample. Precision studies are intended to capture the total test variability from specimen preparation to the final result.

As I said earlier, analytical performance evaluation demonstrates whether the test measures the analyte it's supposed to measure, how correctly it measures the analyte, and how reliably it measures the analyte; whereas, the clinical performance data demonstrates whether this new test result correlates with the target condition of interest in a clinically significant way.

Clinical performance evaluation for a genetic test requires a well-known association between the genetic variants and medical condition. FDA looks for reasonable clinical evidence, that is, whether there is sufficient body of evidence that the genotype is indicated and is linked to the

phenotype. This can be supported by peer-reviewed literature. The sponsor can provide several peer-reviewed journal articles supporting the genotype-phenotype link of each genetic variant to the medical condition; however, these articles should not be referring to the same study population. The articles should also preferably be from different authors. FDA also asks sponsors to provide prevalence information for both pan-ethnic and specific ethnicities.

When there is not enough information or peer-reviewed literature that establishes well-known association between genetic variance and medical condition, sponsor can provide data from clinical studies that identifies the clinical significance of the allele with the medical condition. Case reports and studies without carefully collected phenotype data are generally not acceptable as sufficient evidence of clinical correlation.

For example, for CFDR mutation panel, there is ACOG/ACMG recommendation plus a lot of published literature. This is what FDA used to evaluate whether each allele in the FDA-cleared test is a clinically significant CF causing allele. The literature was evaluated to see whether there is a genotype-phenotype link, and there is sufficient phenotypic information that indicates the severity of the disease.

On the other hand, we are living in the era of new technologies that allows discovery of large amount of novel information that may be clinically useful. For example, if found there is a mutation in a novel

gene can predict risk of developing a cancer in the future, that has to be proven independently in a clinical study.

Once a genetic test is cleared or approved with an established marker, means a marker with sufficient literature support or clinical data support or supported by current U.S. clinical practice guidelines, the next manufacturer who comes with a new test for the same intended use should also demonstrate similar performance with similar clinical sample distributions and types as with the predicate test. Addition of new analytes, for example, addition of an uncommon mutant allele not previously cleared in a test with the same intended use, should meet FDA standard for effectiveness. This can be done by providing sufficient evidence to establish analytical performance of the test with the new allele in addition to providing clinical performance that established that the new allele is indeed of clinical significance.

One last component I want to briefly mention is about the labeling of FDA-cleared or approved genetic tests.

Manufacturers are required to have a labeling that is compliant with the labeling for IVDs, labeling regulations for IVDs. As part of the labeling, the performance of the test, that is, the analytical and clinical performance of the test, are listed in the labeling. Also in general, these prescription genetic tests provide results that require very limited interpretation.

I want to also mention some of the challenges FDA has faced in the evaluation of these prescription genetic tests. One challenge FDA frequently encounters is the lack of clinical samples to cover all the claimed genotypes in the intended use, indications for use. Lack of sample number and sample type could be due to the rarity of the ability to get samples.

Lack of sufficient literature is another challenge. Lack of sufficient literature to support each of the claimed mutations and variants detected by the device. Sometimes there is only one publication to support that allele or sometimes that allele is not identified as a clinically significant disease-causing allele in the literature.

Also another challenge in having clinical specimens from start to end in the analytical studies.

To sum it up, safety and effectiveness of a test is generally determined based on satisfactory analytical performance; clinical performance in the context of use, that is, a demonstration that the diagnostic measurement correlates significantly with the patient's disease or condition; and labeling that is compliant with the labeling regulations for IVDs. And there are other factors such as ability to repeatedly manufacture the device to specifications.

Here are some guidances that are relevant to this talk. I've also provided the link to these guidances here.

Performance of all approved/cleared tests are publicly

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available. I provided the websites here where you can find the decision summaries for all Class II devices and summary of safety and effectiveness for all Class III devices.

This concludes my talk. Thank you for your attention.

DR. WATERSON: Thank you very much. We'll go now to the second speaker, is Marina Kondratovich. Oh, I'm sorry. I missed the dot here. Carol Benson. Excuse me.

MS. BENSON: Good morning. We heard in the previous talk how FDA evaluates genetic tests for prescription use, and I'm going to focus on the principles of FDA regulation for in vitro diagnostic tests for home use.

As an overview, I will start by providing some examples of home use tests. I'll discuss some benefits of home use tests, risks that are associated with home use tests and the mitigation of these risks, the interpretation of the results, the device performance, labeling requirements for home use tests, and how human factors plays a role in home use tests.

On this slide, I've included some examples of some common tests for home use that FDA has cleared. These are some whole blood glucose meters, urine pregnancy tests, urine drugs of abuse, a breath alcohol, and urine tests for ovulation and menopause monitors. You will notice that in each of these tests, the home user must collect the sample themselves, they have to perform the test and they have to interpret the results, and by interpreting the results, I mean they have to read the results

of the test and they have to know what to do with those results, and they have to do all this by reading the labeling that's provided with the test kit.

In this slide, I have some examples of some home use collection kits that FDA has cleared for home use. There's a collection kit for hepatitis C; there's a collection kit for hemoglobin A1c; and there's a collection kit for HIV1 antibodies. In these instances, the home user must collect the sample, but they do not do the testing. The sample is sent to a laboratory for testing.

In the case of the hemoglobin A1c result, the results come back to the user. So the user needs to know how to interpret those results or what to do to follow up. In the case of the hepatitis C kit and the HIV1 kit, the results are phoned to the user, and there's counseling that is available to the user at that time.

There are other home use tests that I've just given you a few examples here, but currently we don't have any genetic tests cleared for home use.

So we might want to know, what are the benefits for a home use test? In determining the benefits, if the test is appropriate for home use, then we might have a condition or a disease that needs to be monitored at home and the best example that I have here is for diabetes. We have home blood glucose meters that are used every day by diabetics to monitor the management of their diabetes. These patients are generally under the

care of a physician and the performance of the meters is sufficient for monitoring glucose. However, there are no glucose meters that are cleared for diagnosis because we don't have performance for this intended use.

Again, in answering what are the benefits for home use tests, we might think, do we have a condition or a disease that can be identified for early detection at home? And the best example that I have here is the urine HCG test that are used for pregnancy. These results of the test are usually given as negative or positive, and the labeling sort of instructs the users to retest if they think that the test is wrong or to see their healthcare provider for follow-up.

When considering the benefits, we might have a condition or a disease that can be screened for at home. An example presented here is the urine drugs of abuse test for screening of certain drugs. However, the results of screening tests are not definitive. So confirmation testing is needed, and the risk of this screening test is mitigated by the labeling instructing the user to send a sample to a laboratory for confirmation. And in the labeling, the instructions are given as to where and how to send a sample for confirmation at the laboratory.

Home use tests have risks. These include false results, incorrect interpretation of the results, failure of the user to follow directions, and unreliable test kits. In evaluating the risk of home use tests, we believe that some risks can be mitigated when the device is robust, it's

simple, it works correctly every time, and it's not easily affected by the environment or the use of different operators.

FDA evaluates the complete test system in a user study to see if the home user can read the instructions, collect the sample, perform the test, get accurate results, interpret those results using only the labeling that's provided in the test kit.

An important aspect of the safety and effectiveness of the test is the interpretation of the results by the home user. After the home user has performed the test, they need to know what to do with the results by reading the labeling; therefore, the instructions must be clear about what the user should do. Sometimes the labeling instructs the user to contact their healthcare provider. Sometimes the user is instructed to collect another sample to retest now. Sometimes the user is instructed to test again on another day if they question the results. However, there is a risk that the user may not suspect that the test is wrong and therefore not seek treatment or contact their healthcare provider.

In assessing the risk of false or inaccurate results for a home user, we want to know the impact of safety and effectiveness of the test, for example, the false result causes the home user not to seek treatment when they need to or the false result causes a delay in seeking treatment, or the user can self-manage their condition improperly, or the user does not follow up with a healthcare provider when they need to, or the user experiences

unnecessary worry about the test results, or the user has a false sense of security and does not follow up with a healthcare provider when they should.

So in evaluating the risks, if the benefits and the mitigations of these risks tip the scale so that they outweigh the risks, then we proceed with the evaluation of the performance of the home use test in the hands of the home user.

The performance of the test in the hands of the typical home user is evaluated in what we call a home user study. The users should be from various backgrounds and have no experience in testing kits, and they have to use only the labeling that's provided with the test kit to perform the testing. The test results of the home user are compared to a laboratory method for accuracy. However, how much accuracy is needed or will the test work at home depends upon the benefits of the tests versus the risk and the mitigation of the risk as well as the likelihood of an incorrect result. Sometimes the needed accuracy and likelihood of an incorrect result is known and sometimes it is not known.

The labeling is evaluated in the home user study to determine if the home user then can read the directions for use without any assistance and perform the test. Another important aspect of the labeling then is the interpretation of the results. After the user reads the results, they need to know what to do with those results.

Questionnaires are given to the users to answer that can capture how well the user understood the directions and how easy the users think the test was to performance.

FDA evaluates the labeling for home use by requesting that the instructions be written generally at about an eighth grade reading level with pictures and diagrams on how to get a sample and perform the test. Pictures are also good for interpreting the results for many tests with built-in QC lines. Users can refer to the pictures when determining if the test did not work or the test results are invalid. Since some tests give lines for positive results and some do not, then pictures are very helpful in these situations.

Also in interpreting the results, the user needs to know what to do for a safe and effective test. Does the user know to seek care, not to seek care, repeat the test, get a new sample and repeat the test, or talk to their healthcare provider? And the telephone number is given in the labeling in which the user can contact someone at the company if they have questions about the test kit.

You may wonder how human factors plays a role in home use tests. People have different abilities to read and follow directions. Home users are not trained so they have no built-in good laboratory practice standard that the laboratorians do. What can go wrong may go wrong in the home use setting. Therefore, home users need robust devices that are

simple, they're reliable and they give accurate results, and that they can interpret the results, for the test to be safe and effective.

So, in summary, FDA does regulate home use tests, whether they are a complete test kit or only a sample collection kit. The benefits and risks, along with the mitigation of risks, are evaluated for safe and effective use. Of importance is the interpretation of the result by the home user -- they have to know what to do with those results -- and the performance of the test, the accuracy, the performance versus a laboratory method. If the home use test can be found safe and effective, the labeling needs to be clear and concise and contain pictures.

We have learned that human factors play a role in the safe and effective use of home tests because what can go wrong may go wrong with untrained home users. However, with robust tests that are simple and accurate, home users can have a safe and effective test.

In this slide, I've given you the website to search. We have a database for home use tests. On the website, we call these OTC or over-the-counter test. They are the same tests that I've been talking about today as home use tests. Thank you.

DR. WATERSON: The final speaker for this morning will be Marina Kondratovich.

DR. KONDRATOVICH: Good morning. In my presentation, I will speak about risk assessment tests. First, please note that I will speak not

about all DTC tests today but mainly about DTC risk assessment tests.

Second, it's not about all risk assessment because, for example, we can have ultrasound tests for measuring osteoporosis. So risk assessment tests has a lot of different values, but in my presentation, I will speak only about DTC risk assessment tests.

So I will start with introduction of the basic scheme of DTC risk assessment test. Then I will discuss basic concept like risk, relative risk, likelihood ratio, odds ratio. Then I will discuss more details about typical DTC risk assessment test, and then I will finish with few words about clinical validation.

So we can see the DTC risk assessment test. Another name is pre-dispositional test/susceptibility test that estimate the risk, relative or absolute, that an individual will develop a condition during the lifetime. For example, test for Alzheimer's disease, test for prostate cancer, test for type 2 diabetes.

Possible intended use claim: to estimate the likelihood that individual will develop target condition -- target condition is, in plain language, disease -- during the lifetime.

The basic scheme of the typical DTC risk assessment test is following. So we have individual and for the sake of simplicity consider that the test is measured in only four markers, four SNPs: SNP 1, 2, 3, and 4. From this patient, from this individual, there are collected only usually two

variables, sometimes it's three. Usually it's only race, gender and sometimes it's age. So this information from race, gender and results of the four markers go into some kind of like assessment or interpretation algorithm, and this interpretation algorithm provides four output of the test. Please note that from the FDA point of view, entire system, the entire system is the test, which started from the collection of the sample, measuring of the markers, then all this information from the markers to covariates go into the interpretation algorithm and provided four outputs.

What kind of four outputs? First is provided pre-test risk or another name is average risk. Because collected only two covariates, race and gender, this pre-test risk is really race and gender specific. For example, if the gender is male, race European, pre-test risk is 20 percent.

Another output is relative risk. For example, 1.5. Another output of this device is absolute risk, 30 percent in this example, 20 multiplied by 1.5. Also provided are risk category as low, average and high, for example, in this high.

Let us consider basic concept related to the DTC risk assessment: absolute risk, relative risk, likelihood ratio, odds ratio, and then because DTC risk assessment test has more than two outputs, then we need to consider test with more than two outcomes. All these concepts really can be introduced with very simple tests, with how we call qualitative tests with two outcomes, tests which have only two results: positive and negative.

Let us have 500 subjects who are representative subjects from the intended use population, target population. So we have 500 subjects. Each subject has results of the clinical reference standard, or another term, gold standard. So for every subject, we know results, target condition present or target condition absent.

In this example, we have 100 subjects with disease and 400 subjects without disease. Also for every subject, we have results of the tests, positive and negative. Please note that here prevalence, 20 percent, that 100 subjects among 500 have disease, really reflects prevalence in the intended use population because we selected random sample from the intended use population.

We know how clinical performance of this test is described. It is described by sensitivity and specificity. For sensitivity, we're calculating percent of the subjects who have positive results among all disease, and for specificity, we calculated percent of the subjects who have negative results among all subjects without disease. But there are another way to describe performance of the test which are more clinically relevant and related to the predictive values.

In our example, we have 230 subjects with positive test results. What is the probability that among the subjects there are diseased people? What is the risk to have disease if the person has positive test results? Another name for this is the positive predictive value. We have 230

subjects with positive test results and among them, 70 have disease. So risk of disease for the positive test results is 30.4, 70 divided by 230.

Also, we can calculate in a similar way what is the risk to have disease if the test results for this subject is negative? We have 270 subjects with negative test results. Among them, there are 30 with disease. So 30 divided by 270 is the risk to have disease if the test results are negative. This is really 1 minus negative predictive value because for negative predictive value you're really calculating subjects without disease among all subjects with negative test results.

Here a very important characteristic of this population is pre-test risk of disease, and there are a variety of terms which describe this same concept, like baseline risk, prevalence, average risk. So all these terms describing the same, pre-test risk of disease. And in our example, it will be 20 percent, 100 divided by 500.

So we have two risks which related to the test results and we have pre-test risk. We can compare this risk among the different risks and also relative to the pre-test risk. So we can compare risk of disease for the subject with positive test results with regard to the pre-test risk. So this will be an absolute risk divided by pi. It will be 1.52, 30.4 divided by 20, and the meaning of this is that the subject with positive test results, the risk for this subject increases by 1.52 times with regard to the pre-test risk.

In similar way, we can calculate the relative risk of the

negative test results to the average risk. This risk will be 0.56, so 11.1 divided for the pre-test risk, and the meaning of this is that for the subject with negative test results, the risk increases by 0.56 times. In reality, if your relative risk is less than 1, you can tell that it is decreased by some number.

Also we can calculate relative risk with comparing risk for the positive test results versus risk for the negative test results. So here it will be 2.74. So I'm comparing the 30.4 to 11.1. And the meaning of this is that the subject with positive test results, for this subject, the risk increases by 2.7 times with regard to the subject with negative test results. So we have relative risk which related to the pre-test risk and also we can compare risk between positive and negative subject.

Absolute risk and relative risk depend on the sensitivity and specificity, but for our talk, it is the most important that it also depends on the pre-test risk. Really it's easy to understand why absolute risk really depends on the pre-test risk on the prevalence, because when we calculated sensitivity and specificity, we're really doing our calculations in the columns, but when we're doing calculation for the risk, we're working in the rows. So like we're working in the first line for the positive test results and the second line for the negative test results, and in this situation it's really important, what is the percent of the disease positive among entire population?

In addition, even the relative risk is also dependent on the pre-test risk. In this simple example, when we have that our pre-test risk is 20

percent and sensitivity/specificity is 70 and 60 percent, correspondingly, so we have that absolute risk will be 30.4, 11.1, and this is our relative risk what we saw: 1.52, 0.56 and 2.74.

Consider that were increased pre-test risk, instead of 20 percent, we have 40 percent, but the performance of the test is absolutely the same: 70 percent sensitivity; specificity is 60 percent. When we're doing this calculation, we see that, yes, absolute risk are increased but also relative risks are also different. For example, for the absolute risk for the positive test results relative to the average, for 20 percent, we have 1.52; and for the 40 percent, we have 1.35. For the 20 percent, when we're comparing risk of the negative results to the average, our relative risk is for 20 percent, pre-test risk is 0.56, and for the 40 percent, 0.63. So relative risk also depends on the pre-test risk.

But there are another concept: likelihood ratio and odds ratio, which really has a lot of advantages. And one of the advantages is that it really does not depend on the pre-test risk. But likelihood ratio related not to the risk by itself, but to the concept of odds. Odds are the ratio of the probability of one outcome to the probability of its opposite outcome. For example, if we consider single coin without a head and tail, then odds equal 1. Why? Because we have two outcomes: probability of outcome head is 0.5. Probability of opposite outcome is 1 minus 0.5. So odds will be 1.

If we have subject from intended use population with pre-test risk  $\pi$ , for this subject, there are two outcomes: disease and non-disease. Probability of outcome disease is the prevalence, pre-test risk  $\pi$ . So pre-test odds will be ratio of probability of this outcome to the probability of opposite outcome. So  $\pi$  divided by  $1 - \pi$ .

After the test is performed, with the knowledge of the test results, we also can calculate odds. It will be called post-test odds. And here, we have positive test results and negative test results so we can calculate two post-test odds.

Post-test odds are we need to consider probability of the outcome disease for the subject who have positive test results. This is our absolute risk. So post-test odds for the positive test results is risk divided by  $1 - \text{risk}$ , risk related to this subject who have positive test results. And for the post-test odds with negative test results, it will be absolute risk for the subject with negative test results divided by  $1 - \text{absolute risk}$ .

Is there are some relationship between post-test odds and pre-test odds? So we have pre-test odds and two post-test odds. Doing some mathematics, we can obtain that this relationship exists, and this relationship can be presented by this formula in the green rectangle. If we have pre-test odds and post-test odds, relationship is very simple. You need to multiply by some multiplier, which is called likelihood ratio, and because we have two post-test odds, we have two likelihood ratios. One is likelihood

ratio for the positive test results, sensitivity divided by 1 minus specificity; and likelihood ratio for negative test results, 1 minus sensitivity divided by specificity.

So this is our basic formula which will be very useful for understanding how the DTC risk assessment tests produce results.

But another very important point that likelihood ratio, you can see that it depends only on sensitivity and specificity. So likelihood ratio does not depend on the pre-test risk.

We can calculate post-test odds for the positive results with regard to the post-test odds for the negative test results. So likelihood ratio produce post-test odds with regard to the pre-test. But we can compare post-test odds for the positive test to the post-test odds for the negative test results. Then it's easy to see that it's produced ratio of this likelihood ratios. So odds ratio is the likelihood ratio for the positive test results divided by likelihood ratio for the negative test results, and odds ratio also does not depend on the pre-test risk.

Consider tests with more than two outcomes. In the hypothetical example, the test measures four markers. Each marker has three possible results: aa, Aa, AA. Then the test with these four markers has 81 possible results. So we have three results for marker 1, three results for marker 2, three results for marker 3, and three results for marker 4. So total number of the different combination will be 81.

For the sake of simplicity, consider test with three outcomes, like results 1, 2, and 3. Let us have 500 subjects who are representative subjects from the intended use population, and each subject has results of the tests and results of the gold standard, and prevalence is 20 percent, reflect prevalence in the intended use population.

So the following table presents performance of the test, if the test has three results -- not two how we consider, but three: results 3, 2, and 1. How we present in this performance? We have 100 subjects with disease and we provided results for all these disease subjects. How many subjects have result 3? How many subjects have result 2, 1? Similar for the subject without disease.

So we can calculate risk of disease for the subject who have result 3. It will be 25 percent among all 96 subjects with result 3; 24 have disease. We can calculate the risk of disease for the subject who have result 2. This is total number of all subjects with this result, and this is number of the subject with disease. We also can calculate in similar way risk for the subject with result 1, and also we have pre-test risk. So we have pre-test odds which are related to our prevalence, and we have three post-test odds, for result 3, result 2, and result 1, and all these post-test odds are really related to the absolute risk.

So the same question: Is there a relationship between post-test odds and pre-test odds? And it can be demonstrated that relationship is

absolutely the same like for the qualitative test with two outcomes. So it does not matter. You have test with two outcomes, you have test with multiple outcomes, relationship between post-test odds and pre-test odds is absolutely the same. You need to multiply pre-test odds by corresponding likelihood ratio and then you obtain post-test odds.

Likelihood ratio of corresponding results is presented in a ratio: how frequently you have results among subjects with disease to how frequently you have these results among the subjects without disease. And in our example, in order to calculate this first frequency, we consider what is the percent of the results among the subjects with disease, like 24, 56, 20. Like for example, among disease positives, the most frequent results is result 2, 56 percent.

Similar way, we can do percent of the results for the subjects without disease. For example, the most frequent results among subjects without disease is result 2. Then we calculated likelihood ratio, a ratio of how frequently this test result among the subjects with disease and how frequently this test result among the subjects without disease. So we have likelihood ratio, 1.33, 1.04, and 0.61. And if you compare to the risk and to the pre-test, you see that likelihood ratio is like way of quantifying how much given test results change the pre-test baseline risk of the target condition.

For example, if I see that pre-test risk is 20 percent and for

result 2, risk is 20.6. So there is almost no increase in the risk. And similar type of information I'm obtaining from the likelihood ratio. I see that likelihood ratio for result 2 is 1.04. So it's almost like there are no increase in the risk.

Odds ratio, we have three likelihood ratios and we can calculate possible ratios between these likelihood ratios, but usually it's very convenient to consider likelihood ratio and how they related to the results with the lowest risk, so normalized to some kind of lowest risk.

In our example, results 1 give me a subject with lowest risk among population because for this subject, we have a risk, 33 percent. So I consider this is like baseline, and then I consider odds ratio like I'm comparing how more frequently, how more increasing risk for the subject with result 2 compared to the subject with result 1? How more risk increase for the subject with the result 3 compared to the result 1? Of course, I can compare also to result 2, but usually it's very convenient to compare to the lowest risk, result 1. So likelihood ratio are related to the average pre-test risk, and when you speak about odds ratio, usually it's related to the lowest risk in your population.

In summary, risk and relative risk depend on corresponding likelihood ratio and pre-test risk. Because risk and relative risk depend on the pre-test risk, in some study designs they cannot be estimated, for example, in case-control studies when your pre-test risk does not reflect

prevalence in the intended use population.

Risk and relative risk measure probabilities of events in a way that is interpretable and consistent with how people think.

With regard to the likelihood ratio and odds ratio, likelihood ratio and odds ratio do not depend on the pre-test risk. Because they do not depend on the pre-test risk, they can be calculated even in the case-control studies. It is easy to adjust odds ratio for other variables through like logistic regression, but likelihood ratio and odds ratio are more difficult for interpretation because they are related to the pre-test odds, post-test odds, which are not intuitive.

Right now let us consider a typical DTC risk assessment test in more detail. For the sake of simplicity, consider a test which measure four markers, four SNPs. So how we discussed already, each marker has three possible results, then our test produce 81 possible results.

Consider that some individual has test results. So for the  $A_i$  results for the first marker,  $B_j$  results for the second marker,  $C_k$  for the third marker and  $D_l$  for the fourth marker. So this is the results of the four markers for this particular individual.

Basic idea of the calculation of the risk for this individual using typical DTC risk assessment tool is following: that shows this formula, that post-test odds are equal likelihood ratio, corresponding multiplied by pre-test odds. So our pre-test odds, it's really related to our pre-test risk. Then

we need to know likelihood ratio. Then we multiply this pre-test odds and we're obtaining odds which related to the risk of this subject. So we need to know our pre-test risk, likelihood ratio and then we can obtain risk for this subject.

So let us discuss in more details all components of this formula. Let us start with likelihood ratio. For given race, our information from the case-control studies in published literature used, usually the papers which are independent confirmation of GWAS. Please note that we consider given race/ethnicity. So your paper should have information from case-control study about odds ratio which related to this race. If there are no such kind of papers, then you don't know what is the likelihood ratio for this particular race.

There are some issues related to this, how the published literature is used. Even for the same set of published papers related to the target condition disease, different markers, different SNPs can be included in the test because different approaches for selection of the SNPs are used by different developers of this test. It can be different approaches. For example, somebody can consider that it should be at least one paper after GWAS study; somebody can consider at least two papers, and even here you started to see some inconsistencies, which SNPs will be included in the test.

Second issue, even for the same set of published papers and for the same SNP which included in the test, different odds ratio estimates

can be used in the calculations of the likelihood ratio because different approaches can be used. For example, hypothetical example, we have paper 1 and this paper produce odds ratio 1.2. In paper 2, we have odds ratio 1.4. In paper 3, we have odds ratio 1.1. What kind of odds ratio we need to select for the calculation of likelihood ratio in the device? It can be different approaches. For example, you can select study with larger sample size or you can do some meta-analysis on like averaged, and you can obtain slightly different results, even based on the same set of papers.

Information about odds ratio in the case-control studies is used for calculation of likelihood ratio, and different assumption also can be considered because in the paper, usually provided odds ratio relative to the lowest risk. And here we need to know our likelihood ratio which are related to the average risk.

So how you transform this information, it also requires some kind of assumption. For example, sometimes there are some assumptions that controls are really not subjects without disease but a random sample from population, that among your controls also there are subjects with disease. For example, if you're not applying your gold standard very vigorously to your control, maybe it's some kind of correct assumption but definitely it's not always correct assumption.

So we discussed likelihood ratio for one marker, but we have four markers in our hypothetical example. So for the subject, we have

results for each marker and we need to know likelihood ratio for this combined effect of all four markers. Every time for defining likelihood ratio for all of these four markers, there are assumptions that all four SNPs are independent, like no interaction. It's called multiplicative model. Of course, this assumption may not be correct. If we consider examples that for SNP 1, for this results, for example, Aa, likelihood ratio 1.05; for second marker with results BB, likelihood ratio 1.27; for third marker 0.77 because we have results cc; and for the fourth marker, we have likelihood ratio 1.55, then in all these DTC risk assessment tests, likelihood ratio is calculated by simple multiplication which may be not correct always. So in this example, it's 1.59.

Let us discuss in more details pre-test risk. So we discussed multiplier, likelihood ratio, what kind of issue we had, but we have second part of this formula, pre-test risk  $\pi$ .

Absolute risk is calculated based on corresponding likelihood ratio in pre-test risk, and pre-test risk is provided based on the publicly available information about race- and gender-specific lifetime risk, for example, Surveillance Epidemiology and End Results Cancer Statistics Review.

But pre-test risk, average risk, is gender- and race-specific. So it's really very limited number of factors. The average risk present risk averaged over all other important risk factors, such as family history, smoking, environmental factors. So please pay attention, like family history

is not included when I'm considering covariates of the subjects. So it's only race and gender. Sometimes it's age also.

So individual pre-test risk taking into account other important factors can be very different from the average risk. Consider hypothetical example, that how it affects this pre-test risk. For example, consider like lung cancer, and for the lung cancer in this hypothetical example average risk is 20 percent. Average risk for the same race and gender -- that is all, only race and gender. But among the subjects, there are people who are smoking and people who are not smoking, and this is really very important risk factor. So even the average pre-test risk is 20 percent, there are some people who have maybe 5 percent of the risk because they are not smokers, and there are people who have 35 percent of the risk because they are smokers.

So let us consider how this pre-test risk affecting calculation of the DTC risk assessment test. Consider that even likelihood ratio is the same, 1.5. If the subjects have pre-test risk 5 percent, then post-test risk is 7.3 percent, and this formula is very simple. Yes? This is our pre-test odds, post-test odds, and I'm multiplying by 1.5 and obtaining what is my absolute risk.

So for the subject with pre-test risk of 5 percent, absolute risk is 7.3 percent, and relative risk, which is 7.3 divided by 5, is 1.46. For the subjects who are completely average, 20 percent of pre-test risk, post-test

risk is 27.3 percent and relative risk is 27.3 divided by 20, so 1.36. We know that relative risk is also dependent on the pre-test risk. And for the subject with 35 percent of the pre-test risk, post-test risk, absolute risk will be 44.7 percent and relative risk will be 44.7 divided by 35, 1.28.

So absolute values of the post-test risk are considerably affected by the pre-test risk. In our hypothetical example, with likelihood ratio of 1.5, and pre-test average risk of 20 percent, but the range of the individual risk, for example, from 5 to 35, post-test risk can be from 7 percent to 45 percent. Relative risk are also affected by the pre-test risk but to a much lesser degree. In our example, average relative risk were from 1.28 to 1.46 when my likelihood ratio was 1.5.

If the pre-test risk is very low, if you have very rare disease, like very, very few percent, close to almost like mathematically to 0, then relative risk equal likelihood ratio. In this situation, your relative risk does not depend more on your pre-test risk and relative risk. It's very close to the likelihood ratio, but this is only if your pre-test risk is very small.

If you make assumption that your controls are not subjects without disease, but the random sample from the intended population, then it's also assumption that your relative risk is almost equal to the likelihood ratio. So in some tests we saw that kind of assumption, that your relative risk is almost the same like your likelihood ratio. But, again, in general, it is not correct statement because relative risk depends on the pre-test risk and

likelihood ratio does not depend, and in the paper you have likelihood ratios.

Let us discuss risk categories because how we remember this test produce not only pre-test risk, relative risk, absolute risk, but also risk category like low, average and high. Various approaches based on relative risk or likelihood ratio or absolute risk can be used and these different approaches can produce slightly different categories. Of course, if you have different cutoffs for defining what is mean average, you also have inconsistent results among different tests.

Consider, for example, that we have pre-test risk of 20 percent and we establish in category average based on the likelihood ratios. Likelihood ratio for the low and average is a cutoff like 0.8, and cutoff for the category average between high is 1.2. Then we can show that this cutoff 0.8, which are based on the likelihood ratio, is equivalent to the cutoff between low and average, 0.833, if you consider relative risk.

And similar way, if your cutoff 1.2 between average and high category, based on the likelihood ratio you have, then this cutoff is equivalent to the cutoff 1.154 if you use relative risk for defining average and high. In similar way, if you use defining category based on the absolute risk.

So these different approaches can produce that the same person can be classified into different risk categories because some

developers can use different approaches how they define categories, what is mean average, what is mean low, what is mean high.

Let me say a few words about clinical validation. DTC risk assessment test reports absolute risk for individual. Note that with regard to the study design, the absolute risk cannot be evaluated in the case-control study. So if you have case-control study, it's impossible to evaluate absolute risk. Why? Because for the absolute risk, a clinical validation includes two aspects: discrimination and calibration. The discrimination, we understand the ability of the test to discriminate between subjects who have target condition and subjects who do not have. We would like that the subject with target condition, with disease, have higher values of the absolute risk compared to the absolute risk of the subject without target condition. And for assessing discrimination, a receiver operating characteristic analysis is used. How it's called ROC, ROC curve and area under ROC curve.

In ROC analysis, consider that this red distribution, this is the absolute risk values for the disease group. So all this distribution of absolute values for the subject with disease. And green distribution, this is the absolute risk for the subjects without disease. And when I am constructing ROC curve, I'm really -- started to move cutoff for different absolute risk, and every time I'm calculating what is the percent of the subject below or above this cutoff. So really ROC curve does not use absolute values of the test. It

uses only what is the percent below this -- some kind of cutoff.

So if you have, for example, wrong pre-test or correct pre-test results, your ROC curve will be absolutely the same because it does not matter your absolute values. So ROC analysis discrimination is not enough in order to evaluate test which produce absolute risk. Absolute risk should be well calibrated. If one has 100 subjects and the test is telling that their risk is 12 percent, then one can anticipate that among these 100 subjects, approximately 12 subjects will have the target condition in reality.

So calibration evaluates the degree of correspondence between the risk of the target condition provided by the test. It's called expected, according to the absolute risk by the test, and the actual risk of the target condition. Calibration of the test which provides absolute risk can not be evaluated in the case-control study.

In summary, absolute and relative risk provided by the DTC risk assessment test are calculated based on different approaches that can lead to inconsistencies in the results. Absolute risk depends considerably on the pre-test risk. Absolute risk and the DTC risk assessment test do not include important risk factors, other than markers measured by the DTC risk assessment test and some limited number of factors, as race, gender and sometimes also age.

Thank you very much for your attention.

DR. WATERSON: Thank you. Wow.

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Okay. Does the Panel have any questions for the speakers?

Yes, Ralph.

DR. D'AGOSTINO: I have a number of comments which I think -- I want to reflect or think I'm reflecting some of the discussion yesterday. Marina, congratulations on that presentation. It was very impressive, and I think it helped me in terms of setting in my mind what it is that we're talking about and as a base. And let me just go through a couple of comments and questions which I think reflect at least what I was trying to say yesterday.

When we talk about these risk assessment tests and we talk about race and gender as sort of the covariates, there's so much advancement on a number of fields -- diabetes, cardiovascular -- that it's hard for me to say the only thing you compare it with is some kind of average for the race and gender. I mean we know with diabetes that you don't seem to gain a lot by the genetics, and that wouldn't be done by looking at just yes/no and population rates. It would be done by saying what's your overall glucose tolerance test, what's your family history, and so forth.

So I think I'm concerned, and I don't know if it's the Committee itself, but when you look at these instruments, you look at these tests, you want a risk assessment that builds in knowledge of the fields, knowledge of the different fields that have worked on this.

Another category or another question, and let me rattle them off and then you can respond if you think you need to respond. The risk categories: low, average, high and so forth, when Framingham started looking at cholesterol, if we were looking at average risk -- and I've been producing these risk assessment functions with the phenotypic data, not genetic data, for 30 years now. When you look at these functions, we usually go here's the average risk and here's your risk and you make a comparison. Well, it turns out that, for example, cholesterol was really bad in the population. The average risk isn't necessarily a good risk and you may confound the issue by saying here's the average in the population, here's how much more you are than the average population, as opposed to here's what your risk would be if you were in a normal state, that your blood pressure was normal and your cholesterol was normal, and so forth, and how do you do that. So I'm concerned about these sort of baseline risks being very crude and then these categories based on it.

And when we were building the ATP, the adult treatment panel for cholesterol guidelines, our risk categories were based on economic-type analysis and we said if your Framingham risk was greater than 20 percent for having coronary disease, you should be treated. And that 20 percent came from the rate of a second event, somebody with a MI -- someone with a heart attack, what's the chance they get another heart attack? So I think there's a lot that is floating around that doesn't seem to

be digested in here.

The other thing, just to go on and I'll state it quickly though, is this odds ratio. No one loves the odds ratio more than I do because a lot of mathematical models pull the odds ratio. But I can remember the ApoE type of literature coming out, and these were based on case-control studies, and it looked like if you were, say, ApoE 4, you were doomed to death and so forth. You were going to get a heart attack or you were going to get Alzheimer's disease before you get the heart attack or something like that. And it was only with the cohort studies that this became more and more clear. There's lots of cohort studies. You get these genetic papers now which I participate on, and there will be 100 authors because there's so many seeming cohort studies that are working, and I think that somehow or other the Agency, and I hope our recommendations flow, that we should take advantage of all of that useful information and not just -- and I think your presentation, like I said, was right on target in terms of thinking about these tests, but instead of the baseline risk, what's the risk that we have with certain normal settings? What do you gain beyond the phenotypic data, with the genetics? And I think, I'm hoping -- I mean, you're nodding approval, I think, so I think you understand what I'm saying. And I think all of that -- and I think we were trying to get that across yesterday, and I think your presentation with the methods and so forth really puts it right on the table. We need more than these sort of baseline risks that you're talking

about for us -- for me to feel comfortable about these tests. Thank you.

DR. KONDRATOVICH: In my presentation, it was, you're absolutely right, current status, how they're doing right now. It's not like how we suggest. I agree with all your suggestions, but presentation, it's exactly -- you're on the point that it's race and gender, sometimes age, that is all what we have. And I showed how pre-test risk can be different in reality. So it's very difficult even to do this interpretation for the person, what is mean above average or below average.

DR. D'AGOSTINO: And just one last comment. I had a discussion yesterday with one of the presenters about the calibration and so forth, and I was trying to get across that I don't know what you mean by calibration with relative risk; calibration is absolute risk and so forth. And I think that the discussion, not correct or incorrect, but it reflects sort of a misunderstanding or conglomeration of a lot of ideas, and we need to sort of sort them out in a very careful way. Thank you.

DR. WATERSON: There are a lot of people that want to comment. I'll start over on this side and just kind of go around.

DR. DAVIS: Margaret Davis, good morning. Thank you. My question is just a basic one. As I paraphrase a famous statement, we are prone to repeat history if we are unaware of it or forget it. So my question is what moved the FDA to begin regulating the prescription genetic tests? Was it to protect the consumer because of insensitivity, because of

unscrupulousness? That's Reena. Is it Reena?

DR. GUTIERREZ: So let me take that on. Actually the FDA regulates all tests no matter if they're genetic or not. So we started regulating in 1976, and what moved the FDA to regulate tests, in vitro diagnostic tests, is that they believed that they needed to have a certain amount of safety and effectiveness assured by an independent assessment before they went into market.

Traditionally, if you look back historically, the first tests that were regulated by the Agency were the antimicrobial susceptibility because they definitely had a very strong correlation as to whether the antibiotics were working or not, and they were regulated originally by drugs.

DR. DAVIS: So basically we are considering that same thing right now?

DR. GUTIERREZ: That's correct. Congress gave the Agency then, in 1976, the responsibility to regulate all in vitro diagnostic tests and genetics, which started a little later than that, are included as diagnostic tests.

DR. HEJAZI: Yeah, with respect to the same, just to follow on that, as the Agency continues to regulate some of these genetic testing, are they going to be similar like a Class II device? And if that's the case, when there are no predicate, how would the Agency handle that? Would it be under a de novo device, for example? Just any comments on that would be

helpful.

DR. GUTIERREZ: So the Agency regulates based on risk. In some of these direct-to-consumer genetic tests, they are likely to be considered medical devices because they relate to health, but they may be of so low risk that we may consider some of them to be Class I. There's a possibility that some of the intended uses would be that.

We would try to find ways to not make a lot of work for ourselves and get them to the correct risk the best way we can. Down regulating is never easy, but there are ways to move that along. We have, you know, we have even considered at some point, for example, when we've been talking about laboratory-developed tests, we've even considered putting panels together that will help us set the correct regulations. So there are ways for us to manage that.

DR. WATERSON: Majid.

DR. MORIDANI: I have a general, technical question. I kind of understand how ROC curves are built for quantitative biomarkers, but I quite do not understand how we can build a ROC curve for a genetic test that we are just looking at if SNPs is present or not present.

DR. KONDRATOVICH: Okay. If you have biomarker or marker only with two outcomes, then your ROC curve is very simple; it's one point. And it's really area under ROC curve sensitivity plus specificity divided by 2. But this test are slightly more complex.

First, one marker has three results, yes, and imagine that you have right now four markers. You already have 81 results. Some tests can have, for example, 20 markers. So it will be 3 in the power of 20. So you have a lot of different values, theoretically, at least. Some may be very similar. So you can create ROC curve because you started to have a lot of different values. So, of course, it's not quantitative. You're absolutely right, but it's like a lot of values which you can use in order to create this ROC curve.

DR. WATERSON: Rochelle.

DR. HIRSCHHORN: This is I think applicable to many things we've discussed. You talk about race and ethnicity, and I wonder is that self-assessed race and ethnicity, or do you ever use what is very common now --

DR. KONDRATOVICH: No, at least I --

DR. HIRSCHHORN: May I finish?

DR. KONDRATOVICH: -- check how -- I visited websites of the test developers. It's self-reported. Of course, is there is a problem like mixture, race of mixture, so what kind of race you can put and also self-reported, that if you put European instead of African-American or Asian, then it will probably be wrong results.

DR. HIRSCHHORN: Because as you know, there are currently being developed and used markers for different populations. In other words, DNA markers for different --

DR. KONDRATOVICH: Yes, and --

DR. HIRSCHHORN: And does the FDA consider using those or what?

DR. KONDRATOVICH: No, this is not FDA using. This is like we evaluate and test --

DR. HIRSCHHORN: Right.

DR. KONDRATOVICH: -- from the producer. We are not producing any tests.

So, yes, I agree with your idea. Usually if there are different set of the markers for this particular race, then this paper used in order to create like particular set of the markers for this race. And can be opposite situation that there are not any papers related to this race, for example.

You will have one question in your questions which we're planning to discuss with you. So one of the questions is related to this situation when there are no papers related to a particular race.

DR. WATERSON: Dr. Lee.

DR. LEE: Actually along those same lines, I'm just wondering, are there any correction factors necessary for calculating the pre-test based on add mixture populations or is that something that's not necessary anymore?

DR. KONDRATOVICH: Say again your question.

DR. LEE: So, the idea being that the pre-tests are based on

ethnicity as well as --

DR. KONDRATOVICH: Gender, for example. Not always, though. Uh-huh.

DR. LEE: -- the gender. So when you have someone who claims that, you know, their great grandmother is Hispanic. So they have a smaller portion of their genome that's from Hispanic ethnicity. Is there any calculations that are required to adjust that pre-test risk?

DR. KONDRATOVICH: At least I did not -- when I check how this calculation, I do know it's not in that way. You see, this formula is really very, very simple. It's like you are -- for likelihood ratio, it's like you're combining information from the papers. Then you evaluated this pre-test risk. So it's a kind of multiplication. Maybe theoretically it's possible, but not right now. The test doesn't have this approach.

DR. NG: Valerie Ng. I just want to make a couple of comments. Thank you very much for your clear presentations, all of you.

I find it very interesting that -- the conversation yesterday almost brought it up. It kind of didn't make sense to me why people are ordering these tests. They're asymptomatic, which almost by definition means they have a low pre-test probability, and I certainly know in my daily life, which is diagnostic testing, that I tell my house staff don't do any testing unless the pre-test probability is between 30 and 70 percent because a test is not good enough to move you in either direction to make a definitive

diagnosis. So in that regard, I really don't understand, except for curiosity and discretionary dollars, why folks are ordering these tests.

I do want to comment that the people -- these are pretty sophisticated presentations we had today. The level of understanding of statistics, even amongst healthcare professionals, is pretty grim, let alone the average consumer. I have a claim pending for me right now because I recommended not to do a test because a pre-test probability was 100 percent. The patient very clearly had the disease and was treated for that disease, but the patient's angry because she didn't get a test. I said that if you got the test, the likelihood ratio was only 3 or 4, it would have, if anything, clouded the picture.

In terms of having these as over-the-counter or direct-to-consumer testing, again I think the harm is related to perhaps how we present those results and allow the consumer to interpret it.

And then finally, my last comment is a global one related to healthcare costs. And while these are discretionary dollars right now being used, I know down the road, when the rubber hits the road, it's going to come often to a laboratory director to say here's a set of data, how are we going to interpret this? And then related to that will be the legal liability issues based on our interpretations.

DR. GREGG: Yeah, I have a question. Those were excellent presentations. Specifically with the prescription genetic tests, now you went

through very detailed regulatory requirements for getting a test approved by FDA. Yet, in some of these direct-to-consumer tests, those tests are on those panels. How does FDA feel about that, having an FDA-approved test that's gone through rigorous, rigorous requirements, now being on a direct-to-consumer test that perhaps has not gone through that same rigor?

DR. GUTIERREZ: The FDA is on the record as saying that the direct-to-consumer genetic testing should be regulated by the Agency, and we are in the process of helping companies come into compliance, which means they have told us that they will be coming with submissions, and we're working with them as to how they can do so. And part of this meeting is to air out some issues that we're seeing and to try to help the FDA figure out how to navigate that.

In the end, we will be making public -- we usually publish all our reviews -- what were the bases by which we found something substantially equivalent or safe and effective; that is, we would put together a package that will tell you what were the analytic performance that we saw and, you know, what were the risks and benefits that we saw that allow us to clear a particular device.

DR. WATERSON: Please state your name before you speak.

DR. TSONGALIS: Greg Tsongalis. This is for Dr. Philip. You touched on assessing performance characteristics, which as a clinical lab director sometimes gives us a lot of trouble and issues and sleepless nights

because there really aren't guidelines out there that the field considers the gold standard to do this with. And so the examples you gave, like Factor 5 and MTHFR are pretty straightforward, single or a couple of mutations, but it gets a little cloudy when you get to cystic fibrosis with 6 mutations, 23 mutations, 43 mutations, 60 mutations, full gene sequencing. And so with a lot of the things that we're talking about for direct-to-consumer testing, we're talking about very, very high complexity, high throughput types of technologies, the microarrays, next gen sequencing. How in the world are you going to plan on evaluating performance of millions of SNPs at the same time?

And I think it would behoove the FDA, not just for direct-to-consumer testing, but for also other approved tests that we run in the clinical lab, to make sure that there's adequate calibrators and control materials before these tests are approved.

DR. PHILIP: That's a very good question. So we know we are going to face that reality that, you know, whole genome sequencing is going to be on the door, and so we have started working on the analytical validation for that technology.

And regarding the clinical indications, like what I mentioned in my talk, we look at -- for example, the ones we have cleared, we have so far cleared 60 mutations for CF. So we had strict criteria when we looked at those mutations, and we can see in the future we will be looking at more

mutations and clearing those, but so far what we have been doing is what I presented.

So we will look at the analytical validation for whole genome sequencing or, you know, the technologies that's going to come in the future and we will be looking at them and I'm sure we will have a ways to go, and this Panel hopefully in the afternoon, I'm hoping will give us some input for the analytical and clinical validation for these kinds of tests.

DR. MAHOWALD: This is also for you, Dr. Philip. I'm still trying to get a handle on clinically significant results. In particular, Dr. Ng was talking about late onset susceptibility kinds of tests or tests which are unnecessary because we already know the status. And I know you, I think in your talk, related this to the intended use, and in your slide on that topic, you indicated that the intended use refers to the clinical indications. So would you explain to me more fully the range of situations that constitute clinical use and, in particular, those situations where there's a non-symptomatic individual whose expectation for any reasonable assessment of expectations is far into the future? How is that clinically significant now?

DR. PHILIP: Okay. So, yes. In the intended use of the cleared, approved genetic tests, we have indicated a clinical indication. For example, the one for CF will say it is for carrier testing or whatever. But for the ones which may be asymptomatic population, we will have to lay out intended use for like the general screening that could be an asymptomatic population.

And for the clinically, as far as our regulation, what we look at is whether in a target population, whether the use of this test will give clinically significant results. That's what we look at, and how do we -- yeah?

DR. MAHOWALD: How is it clinically significant for someone who could not become symptomatic for decades? How is that clinically significant?

DR. PHILIP: Yes. So, for example, for --

DR. MAHOWALD: Or is already symptomatic and so diagnosed.

DR. PHILIP: Well, for example, if you give that kind of claim, then it's actually for a prevention claim, right. So that's --

DR. MAHOWALD: Not always. Some.

DR. PHILIP: Yes, for some. That's what I, you know -- so some of them could be a prevention claim. So that's actually clinically significant when we -- you know, in the indications.

DR. MAHOWALD: Maybe Dr. Hersch wants to comment on the clinical significance, for example, of -- the clinical significance, you might say for psychological reasons, for onset of Huntington's in a very young person?

DR. HERSCH: I think future risk is clinically significant. This is Steve Hersch. Future risk can certainly be clinically significant because it leads people to make all kinds of decisions about what they do and also as, you know, diseases -- we don't know when a lot of diseases start and so, for example, a disease like Huntington's disease, where there's changes in the

brain decades before there's any clinical symptoms, you know, it lets people know the potential for doing something during these prodromal periods. So there are clinically significant information to draw from diagnoses in advance, just as that as an example.

DR. WATERSON: David.

DR. RANSOHOFF: David Ransohoff. I was struck by the tension between Dr. Benson's talk and Dr. Kondratovich's talk in trying to figure out what this means for DTC regulations and so forth.

Dr. Benson seemed to be saying -- you used the words of, the interpretation basically has to be simple and robust, and that boils down to things like a pregnancy test, you're either pregnant or not. You don't have to worry about age and gender and other sorts of things so much and pre-test probabilities when you're trying to interpret it. Same for some of the other tests.

And in contrast, Dr. Kondratovich was explaining the importance of pre-test odds or pre-test probability and likelihood ratios and so forth, basic bread and butter for clinical epidemiology in medical school, but as Dr. Ng said, medical students don't understand it and practicing docs don't understand it, and so presumably this is all going to have to get digested by the sponsor before it ever gets to a consumer because we certainly can't expect consumers to do that.

And my question is, does this kind of complexity have

implications for what might be a direct-to-consumer test just because it's so complex and we can't get professionals to understand it, or could this all be mitigated if there's no risk? Is that the way that the FDA might see it? Because it looks inherently that the tests for risk assessment are inherently more complicated because you really do have to think about all these things like pre-test probability and so forth and what does the test result mean. So that inherent complexity is there, but is the idea that if you can't hurt yourself, then we don't really care and people can just do whatever they want with this information? I'm just trying to figure out what this might mean for the FDA.

DR. GUTIERREZ: So I actually think that you are preempting the two questions that are coming.

DR. RANSOHOFF: Is that good or bad? You don't have to answer.

DR. GUTIERREZ: No, that's good. I think an issue for us here will be what are the sponsor responsibilities and what will be truth in labeling to a certain extent? What kind of things can we do to mitigate the risks and to help people understand the test? And to weigh that against, you know, the benefits that are there and the risks that potentially --

DR. RANSOHOFF: And is the idea there if the risk doesn't seem to be very high, then the bar gets lowered and it's just information that people can do what they want with? Is that the kind of idea?

DR. GUTIERREZ: That's correct, but at that point we also need to worry about what is truthful information and how to present it and how do we allow people to understand it.

DR. WATERSON: George.

DR. NETTO: Yes. So it's kind of follow-up and tying in the same thing. So the assumption is these tests, like any other tests, should be regulated to start with, and that's the assumption you've made. And then the assumption is it's going to be at the same rigor. Just because a test, a genetic test is offered DTC, all these measures are going to be still, you know, required to be done exactly the same like it was prescription-wise.

So really the only difference is whether the physician is ordering it and who's interpreting it, right. So these are the two things. And yesterday we talked about possibilities of physician not ordering, but the physician being stuck with a test that they didn't order, trying to interpret it and realizing maybe that wasn't the test I wasn't going to order anyway. So there is that issue. So it's really difficult to disconnect the order from the interpretation it seems like.

And also, it's becoming clear, that every test among these, we cannot do an umbrella decision on these because there are variable tests, the implications are variable. Some can be no risk at all even if you misinterpret it and some can be a lot of gravity to it. So I think ultimately it's going to be every test of this we're going to have to look at independently,

and really the focus should be on the interpretation and orderability, basically. Because the most similar to me from the presentation would be the HIV testing, for example. This is a relatively sophisticated test and the interpretation is still much simpler because you either have it or not according to that kit, but at the same time, there are implications for that. So I think, to me, that's the one that struck me the closest and maybe we can learn certain things from them.

DR. WATERSON: Ira.

DR. LUBIN: So there are some observations I'd like to make. First of all, I want to congratulate all the speakers on exceptional presentations.

One of the take-home messages I got from the last talk was the incredible importance of being able to understand and apply the pre-test risk and, particularly with respect to tests that are predictive, in the sense that perhaps, as was stated, for the majority of the population, if you're asymptomatic, your pre-test risk may be, not necessarily, but may be very low. But if you're not taking into consideration some clinical or preclinical attribute, family history, ancestry or other factors, your pre-test risk may, in fact, be much higher and therefore the relative risk and absolute risk, as defined by some of the companies today, that are returned would be meaningless for the proportion of the population and potentially can lead to misinterpretation of the test. So if I understood, it's critically important that

that information be collected and integrated into the interpretation.

The second point, in regards to some of the literature out there and some that was provided to us as background, with regards to tests that look and combine multiple genetic factors, is how those factors are combined, and there's still debate on whether you get a multiplicative, an additive, or other kinds of effects. And I don't think that this has been resolved or accepted resolved for a majority of what's being looked at today. This is still an active research area.

What this means is that FDA could potentially be given data from different submitters using different methods that are consistent within the population in which they're collecting data for the validation of their tests, but both products on the market may provide some level of inconsistency that could potentially compromise the credibility of use of this technology as we learn more and really want to get it to the point where it is helpful and able to improve health outcomes.

So I think the other issue here is that there are still some facets of the science that still need to be further developed before we have tests, at least in this regard, perhaps, offered to DTC which is even additional interpretative complexities in terms of understanding, you know, that may provide different interpretations through different means of validations, thus compromising how the public views the current and potential future credibility of these tests.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: I just wanted to make two comments that came up along the discussion here. I don't know any physician, and I mean this with all sincerity, who doesn't think of the odds ratio as a relative risk. They're always thinking that when you give an odds ratio, you're giving the relative risk, and that's only true if the probability is very close to 0. So the comments that have been made are extremely important in terms of what you convey.

The other is, Dr. Moridani's question about the ROC. If you turn to slide 28 on the page that was passed out, slide 28, there's a very nice little piece here, and I think -- and let me just play professor for a moment in terms of what the ROC is. If you look at where it says slide 28, and then that first paragraph, it says, "We would like the subjects with target condition having higher values of absolute risk compared to the absolute risk of subjects without target condition." The ROC area is the probability that somebody with the condition gets a higher risk than someone without the condition, and that's the way I think of it. You can look at these graphs, but it's really that will the person with the risk get a higher probability than the person without the risk.

And the other thing is, what we do when we generate these graphs is, if we have as we say, you know, three different outcomes, we plot the points, the sensitivity, 1 minus the specificity, and then we just connect

them with a straight light and color in underneath it. So even with two points, you can draw that graph. And it's a very well used tool and you're right on target in terms of how do I look at it, and I think this probability interpretation is the best interpretation of it. Thank you.

DR. NG: I don't think we should give up hope on the physicians knowing how to use these results. I make mine carry around the nomogram, right. Nobody can do the math, but if you carry around that little nomogram, and I say what's the pre-test probability, and get your straight edge out, it'll tell you what the likelihood ratio of the test is, right. That's our role in life.

And I, in general, tell them likelihood ratios of something up to 5 are pretty much not helpful. Maybe up to 10 is useful, but if it's like 100, like an HIV test, or something, that's really darn good. And they get that real quick. If they see that nomogram and see this range, likelihood ratio of 0 to 5, man, you're not going to move anywhere on that post-test scale, I think they get it big time. So I think our role is to stress the importance of the likelihood ratio, where it becomes relevant, and maybe that's part of the mitigation we would recommend to the producers of these tests.

DR. TSONGALIS: So I think something from Dr. Benson's talk kind of jumped out at me with the home use testing or the home testing, in that there clearly were different categories set up for the different types of tests. And one of them really hopped right off the page at me, and that was

for hemoglobin A1c because it does everything that we're talking about. You know, you have home collection by the patient, you have it sent off to a lab for testing, and then results interpreted by the patient again. These are not trivial results to interpret, maybe not as complex as some of the genetic tests that we're talking about, but clearly I think there's some precedent for having that type of a model set up.

DR. MORIDANI: May I have a comment here? The only difference -- it's a very good example, but the only difference is that for hemoglobin A1c, the patients might request multiple times. So they get educations over times, but in these cases, it's just one-time test. So that's the only distinctions I wanted to bring before the Panel members.

DR. WYNE: Kittie Wyne. You know, the example of A1c is interesting. I don't know how many are sold each year, but I can tell you in general, patients don't do it. They do their fingerstick glucose. They expect us to order the A1c. They don't do the home A1c kit as part of their management. Maybe it's because we haven't taught them to do it, I don't know, but it's not for whatever reason become routine.

I had just a couple of questions and a comment. Back to the issue of the provider, I really think we need to give providers credit. They can understand this information. They can explain it. But how the information gets to the provider is very important. Because I'm very careful to teach my patients to contact me for results of tests, and I tell them if you

don't hear from me within so many days, do not assume it was normal; assume I did not receive the results of the tests. I cannot tell you how many times patients say, well, since you didn't call, I assumed it was normal. So that's something we have to take into consideration.

But with the presentations, I just want to clarify one point from the first presentation. So a prescription test that's approved, such as the CF or such as a RET mutation, if the manufacturer wants to add an additional mutation, they have to submit that test, correct? So if they've got 23 and they want to take it to 24, they can't just pop in the 24th.

DR. PHILIP: They have to submit the test.

DR. WYNE: That's what I thought. I just wanted to clarify. So that's one of the problems because now if we have people doing things with hundreds of different genes and mutations, then the question is do you go through and validate every single one, correct?

DR. PHILIP: That's right.

DR. WYNE: Okay. And then that raises the question that was being asked before about clinically significant. Because I think what we're all struggling with is this whole genotype/phenotype correlation because you told us it has to be clinically significant, that we have to have data to show that it is. And then I'm looking at all these genes that are being run in these panels, and I looked up some of them last night, ones that are relevant to the work that I do, and as far as I knew we didn't have a phenotype

correlation. And I looked up one last night, just checking to see if there's new information and, in fact, a knockout mouse has just been published which has 0 phenotype. So this gene is highly correlated to fatty liver, but the mouse has no phenotype. So we're going to approve that to tell people they're at high risk for fatty liver? I think that's what we're struggling with, with these panels and all these genes.

DR. PHILIP: Well, that's what we are struggling also. So right now, whatever I presented is what we have done in the past. So what we are going forward, you know, maybe could change but it's -- you know, right now I can't tell because this is what we have been doing so far.

DR. WYNE: And this is what Dr. D'Agostino keeps coming back to, is we've got these gene markers but sometimes family history tells me more than these gene markers. And it's not just family history, but my example of this one gene, I can predict better from family history, it turns out, than from that gene of whether or not the person is going to have, not the disease, but the complications from it.

DR. NETTO: So just another issue with the test not being communicated to physician is the inclusion of medical records, and potentially with evolution of tests, if you're taking care of your patients and you have it in the medical record of that patient and realize that the old panel is no longer, that's something that we're going to lose by just giving total control to the patient that, oh, it's negative, so now it's negative.

DR. HIRSCHHORN: I hesitate because I don't remember the whole paper, but there was a recent paper about hemoglobin A1c in which they looked at lowering hemoglobin A1c more than the control group, and the bottom line was that they did not recommend lowering the hemoglobin A1c more. Was it the ACCORD study?

DR. D'AGOSTINO: The ACCORD study. It was killing people.

DR. HIRSCHHORN: It was killing people.

DR. WYNE: No, no, it's not killing people.

DR. D'AGOSTINO: It is true. The death rate was higher in the group that was lowered.

DR. WYNE: Well, but as a statistician, you know that that's the marker that they used. They don't actually have an explanation for the death in that group, and it may have just been an epidemiological blip if they had kept the study going.

DR. D'AGOSTINO: They have a follow-up. They have a follow-up study. They have a follow-up study. They carried it to a 5-year follow-up, and they still get the excess mortality in that group.

DR. WYNE: And they've tried to claim that the excess mortality is due to hypoglycemia and they have absolutely no data to support that. They've tried to attribute it to cardiovascular disease and they haven't been able to support it with that. Another paper that was just published that you're talking about.

DR. D'AGOSTINO: It reduced the MIs. It didn't reduce the overall -- it increased the overall mortality.

DR. WYNE: But the question is what is actually the marker? Is it actually the A1c? Is it the glucose? Is it the people they enrolled in the study? Is it the strategy? I mean, as I said, the A1c is just the marker that they chose to use.

DR. D'AGOSTINO: That was the objective of the study, is to drive down the A1c and that's what they were -- they were lowering the A1c to normal levels and that was related to the excess mortality.

DR. WYNE: But that data is inconsistent with all other studies and the simultaneous studies in other countries. That's the problem.

DR. WATERSON: We'll take one more question here.

DR. NETTO: See, the physicians are not as dumb about such things.

DR. WATERSON: One more question before the break. Any other comments?

Well, why don't we take a 15-minute break then, and we'll resume at 10:30.

(Off the record.)

(On the record.)

DR. WATERSON: Please take your seats.

Okay. I will begin. At this time, we will focus our discussion on

the FDA questions. Copies of the questions are in your folders. In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Dr. Elizabeth Mansfield, Director of the Personalized Medicine Staff, from the Office of In Vitro Diagnostic Devices at the FDA, will read the FDA questions. You may begin.

DR. MANSFIELD: Thank you, Dr. Waterson.

We'll begin today with Question 2 in your packet. The overarching question is: What are possible mitigations against incorrect, misinterpreted, miscommunicated, or misunderstood test results for clinical genetic tests offered through direct-to-consumer testing, without live counseling?

These questions compel you to consider that there will be tests offered through the direct-to-consumer channel.

We'll begin with part (a). Some tests lack established performance characteristics for certain populations. Should some direct-to-consumer tests be offered only to certain consumers (for example, certain ethnic or geographically defined groups)?

DR. WATERSON: Do you want us to go through the category of tests like we did yesterday?

DR. MANSFIELD: I don't think that that's necessary. You can speak more generally if you'd like.

DR. WATERSON: Thank you. Okay. Does anybody want to take this on?

DR. D'AGOSTINO: I think again, translating, or not translating, but using the sort of the risk assessment tools that have been developed in other settings with the phenotypic data such as Framingham and the Gail model and what have you, we oftentimes depend solely on these phenotypic risk factors and we do find that going from one population to the next does introduce problems and quite often in my experience, it's on the absolute risk that when you go from whites in the U.S. to blacks in the U.S., when you go from Framingham population to European population, you find quite often the relative risk hold up, I mean in my experience, the relative risk hold up but the absolute probabilities change. And depending on, do you want to convey an absolute probability to these individuals, then you are in trouble by transporting them without further investigation. But it isn't that they're completely off the wall especially if we have a sense of relative risk.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. But denial of tests based on those reasonings is different than, in fact, mitigating the risk by clarity in the information provided to the patient, labeling carefully to address the issue and, in fact, being transparent in what populations are being used in clarifying.

DR. D'AGOSTINO: I'm sorry for jumping in, but that's what I'm

trying to say, is that you don't want to give up the tests because of this fear that there's a lot of information in it, and presented correctly, you can transmit that.

DR. WATERSON: Colleen.

DR. GALLAGHER: Colleen Gallagher. I think that the target population for the test itself can specialize that. And say, if we develop a test that is for, you know, this particular ethnic group or this particular geographic region, that can be stated in the test, in the design of the test and in its marketing and whatever, rather than having a flat out statement that says, you know, that the FDA should say that tests can only go to certain groups overall.

DR. MAHOWALD: Mary Mahowald. Moreover, the guidelines we got and the definition of clinically significant was that it was based on a target population. So the offering of the validity or the clinical significance is based on that fact. That doesn't preclude it's being offered to the non-targeted part of the population with proper instructions.

DR. SHAMBUREK: Bob Shamburek. I'd agree with that. I think one of it is, if there's truth in labeling, that point will not be as big a one. And if the subject knows a particular disorder, if it's running in families and there haven't been any, that the pre-test probability is going to be very low and they're aware of that, it's basically going to be their money.

But I also think, even though it's not FDA truth in advertising,

we often see misrepresented on the TV, and that's something perhaps the FDA can work with the FTC, but with these particular tests, if the truth in the labeling is there and it can be explained to them and they so choose, then it's probably okay.

DR. WATERSON: It sounds to me that everybody is pretty much in agreement on that point? Yes?

DR. DAVIS: A little more specific -- Margaret Davis, Consumer Rep. As I look at the ads on TV, not particularly for the DTC tests, of course, that's their job because they're there for profit to tell their benefits. I think that when the labeling is done, the limitations should be listed on the label as vigorously as the benefits so that there will be no question about the limitations.

DR. WATERSON: Mary.

DR. MAHOWALD: The other aspect is, at least for those who can afford the test, there would be some pick up in those cases that are not within the targeted population but are surprised, surprised as being expressed in a non-targeted part or, given the range and the ambiguity often of race definitions, the pick up could be increased by allowing that broader availability.

DR. WATERSON: Okay. So I think -- yeah. Ira.

DR. LUBIN: So there's some precedence. I agree with the truth in labeling comments. When the first recommendations came out for

cystic fibrosis, the wording was to be offered and made available and the caveat was we had data on those whom the test was to be made available to, but it was not thought appropriate to close off everyone else in that there may be value at some point or the mutation panel may expand, in which case it might have brought a utility.

There's also different kinds of testing that might be considered, again, that may be handled through truth in labeling. If you're talking about identifying variations that alter the synthesis of a protein that can lead to a clinical condition, the prevalence of that may vary among populations, but if you have a particular variant, it could be a very good indicator that you will get disease. So that's one class.

Another class is a combination of variants to confer risk that may differ among population, and a particular combination may have completely no meaning in one population and a meaning in a second population. But, again, I think that could be handled in truth in labeling and not come across as stigmatizing a particular subpopulation by denial of access.

DR. WATERSON: So it appears that we feel that the tests should be made available on the caveats that have been listed?

DR. MANSFIELD: Thank you. The next question addresses some of what you've already spoken of.

When might provision of information about the risks, benefits,

and limitations of clinical direct-to-consumer genetic tests be sufficient to:

- Enable informed decisions by consumers on whether to order these tests (pre-test information) and/or
- Mitigate the risk that consumers will be misled by or incur harm from acting on test results (that would be post-test information)?

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. I'll pick up where we left off just a moment ago because I think we did enter into this. The conundrum that I see here is the challenge of truth in labeling, open and complete information about the interpretation and transparency versus the context of a proprietary algorithm or method of interpretation. So that I think we're going to have to depend heavily on the FDA in this process because by the very nature of somebody having a proprietary algorithm, that could not be put on the label. So there is a balance there that I think there will be a challenge for.

DR. WATERSON: Margaret.

DR. DAVIS: Margaret Davis, Consumer Rep. Dr. Benson discussed labeling of the prescription drugs that the FDA already regulates, and I thought she made some very valid points. If it's not broke, we shouldn't fix it. That the pictures and the eighth grade reading level should be a part of the labeling because even though some of us have degrees and

we're educated, we still don't understand the jargon of the industry. So I think that those should be considered when they're being labeled.

DR. WATERSON: Bob.

DR. SHAMBUREK: Bob Shamburek. I think also kind of inherent with giving the pre-test risk of saying at the end of this is a low likelihood we're going to find it, I think the post-test testing is going to also be necessary in the sense that the person needs to know when those results come back, there's probably going to be the need for a confirmatory. The low likelihood is likely going to lead to potentially a screening test if you really want to rule out colon cancer or something, and that doubt of the additional cost, again cost is not, but that is a risk that patients or consumers need to know.

DR. WATERSON: Valerie.

DR. NG: Well, I had suggested earlier on the mitigation issue that somehow somebody figure out how to categorize those likelihood ratios into those that aren't meaningful and those that are meaningful, and those get to a physician now or provider now.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: Just to make sure I'm not losing something. Yesterday we spent a lot of time saying that most of these tests shouldn't be done by the consumer. We're not now changing our mind and saying that you could supply enough information, right? I mean yesterday's discussion

is still all valid; is it not?

DR. WATERSON: I think this is sort of a hypothetical if the FDA decides --

DR. D'AGOSTINO: Yeah, exactly.

DR. WATERSON: -- to go ahead and do --

DR. D'AGOSTINO: That's fine.

DR. WATERSON: -- to not accept our initial recommendation, what --

DR. MANSFIELD: That's correct.

DR. NETTO: Yeah, one more question or comment. What happens when the data change? Is there obligations also for previous patients? Because these are, as opposed to a drug that you took and you stop that -- even that I guess there is a follow-up. But in term of your risk change or all that, is there a requirement to recontact these patients because now again the -- your medical record for me is very concerning.

DR. HEJAZI: Yes, and a general question to FDA, as we were discussing about limiting the applicability of these tests, maybe to a subpopulation, would there be consideration of looking at these from a regulatory perspective under HDE? And if so, how would that be handled? Would it be on the basis of prevalence? This is the humanitarian device exemption.

DR. GUTIERREZ: Yeah. I'm not sure that the companies are

actually thinking of limiting their tests to a small enough population that HDE would make sense, and I don't think that the question -- well, first of all, I think that Question (a) was addressed as, you know, these tests are useful even to people who may not be in the particular set. So it's just a matter of how do we then go ahead and label to make sure that it's truthful and the people understand how it applies to them or not.

DR. WATERSON: Tiffany.

MS. HOUSE: Maybe I'm, you know, thinking about it a little bit differently, but in terms of -- say, hypothetically, these tests are available and it's a conversation of how do we best inform patients and make sure that they're understanding what they're getting, and it was my understanding that most of these tests would probably be available over the Internet. And so could the FDA in some way make it a requirement that the ordering process requires some sort of PowerPoint presentation that the patient has to go through and that would, you know, give them at least some sort of education of what they're getting, maybe take a quiz or something, as part of the process of ordering it. And so that way some of the concern that they don't know what they're getting would be allayed.

DR. WATERSON: Valerie.

DR. NG: Is there an expectation -- I was struck by your comment about proprietary algorithms. Is there an expectation that companies measuring the same number of SNPs should generate the same

likelihood ratio?

DR. MANSFIELD: Not necessarily. That will be part of Question 3 later on today.

DR. WATERSON: Colleen.

DR. GALLAGHER: I think that one of the issues is -- you know, we talked about a pre-test versus a post-test kind of thing. I think when you're looking at the possible need for additional screenings or whatever, that should not just be contained in the post-test information, but it should also be part of the pre-test information so that a person who's going to consider having a test knows that it might possibly lead to that before they purchase.

DR. WATERSON: Did you have -- Steven.

DR. HERSCH: I mean, we haven't really gone very much further when talking about mitigations like referrals to clinicians or follow-ups, and I mean there's a lot -- I don't think we necessarily have to discuss sort of -- but I think some of the things that were kind of unstated were oversight over marketing, which I think is different than labeling, but in terms of -- besides all the written caveats about the potential value or lack of value of the tests and the needs for follow up and the potential avenues for follow up and a provision of counseling by companies, all those kinds of things, you can sort of create a big edifice of back up, and I mean I think it's something to grapple with.

DR. RANSOHOFF: Dave Ransohoff. I think we had some good examples of mitigation that to be effective here from Dr. Benson's talk this morning about here's when you go to a doc after you get a certain test result. But I think what this means is, that in considering these tests you may need to consider every single thing on the panel because each one of the test results might have a different implication, and we just heard there's a whole lot of idiosyncratic things about what results mean. The pre-test probabilities could be different for every single marker. The clinical implications could be different for every marker. And just because they're a package, I think you guys are going to have to make some decision about are we judging the package here or all the individual tests? The precedent that as a clinician I would refer to would be -- and it's a lot of work, but this may be life in the big city. When the U.S. Preventive Services Task Force thought about, well, what about the yearly physical exam, which was the first task they took on several decades ago, they deconstructed every single thing in the physical exam. And I'm sort of wondering as we think about panels -- there's individual tests and the panels are made up of lots of individual tests. Are each of the individual tests going to have to be handled in this complex way? And I think it at least ought to be on the FDA's radar.

DR. GUTIERREZ: This is Alberto Gutierrez. I just wanted to make a clarification on labeling. For the FDA, labeling means everything, including advertisements. So it's things that go with the test or even

advertisement, anything that's put out.

DR. DAVIS: Margaret Davis. Pardon me if my question is up in outer space, but how can the consumer be sure that the device detects the genotype it claims to detect? Is that possible?

DR. MANSFIELD: I believe that we're suggesting that our review will provide that insurance -- assurance, I'm sorry.

DR. GUTIERREZ: And I will actually just expand a little bit. Based on our regulations, if we do have a pre-market review, that's one of the things we look at. If the device is considered low risk, Class I, it is up to the manufacturer to assure that they're doing the right thing, and the FDA will inspect and assure that they have done the right things, like determine that they're detecting what they claim they're detecting.

DR. WATERSON: Okay. Mary.

DR. MAHOWALD: Just for my own information, does the FDA also scrutinize TV advertisements for various drugs and mechanisms? Are they really screened --

DR. MANSFIELD: Yes.

DR. MAHOWALD: -- so that they don't misrepresent?

DR. MANSFIELD: For devices, we do not require pre-clearance of advertisements and so on. For drugs, that is sometimes required. For devices, we don't do that; however, we monitor what appears on television, print and other communications.

DR. WATERSON: Okay. Anybody else have any other comments?

Do we want to move on to the next?

DR. MANSFIELD: Yes. Thank you.

We again may have covered some of this, but are there other essential risk mitigation tools that should be provided in providing direct-to-consumer genetic testing?

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. The careful evaluation and potential demand for unlinking test to product. I may sound like an economist here on the one hand or on the other hand. On the one hand, we have pharmacogenetic tests related to the metabolism of a drug that may be critical and appropriate, and we have heard examples, even in the last day and a half, about nutrigenomic tests with the same company offering the products that may or may not be appropriate. So there has to be an examination of that relationship and how one triggers the other.

DR. WATERSON: Any other questions? Comments? Okay.

DR. MANSFIELD: Thank you.

In testing general populations for rare conditions or markers, the false positive rate (otherwise the proportion of positive results that are false) can be significant.

- Should direct-to-consumer genetic test reports recommend

confirmatory or supplemental testing when positive results are obtained for a rare condition or marker?

DR. WATERSON: Go ahead.

DR. MORIDANI: In my opinion, especially when the prevalence is very low, they should recommend confirmatory tests to be offered to the patients because they are at increased risk of psychological and other risks. So the confirmatory test should be considered.

DR. WATERSON: Colleen.

DR. GALLAGHER: Colleen Gallagher. I think one of the things that we saw early on in HIV testing, for example, was a test done in what would now be CLIA laboratories and hospitals, that kind of thing, where it had to be tested three or four times before a result was given. So I think that it falls to the responsibility of the companies in a sense to make sure that they confirm what they provide, but at the same time I think that, you know, FDA might consider making sure that laboratories are CLIA laboratories, things like that, so that those kind of standards already exist within the laboratories being used.

DR. WATERSON: Greg.

DR. TSONGALIS: Yes, so I want to echo along the same lines on the confirmatory testing. You have to be careful about recommendations because will it be done by the same laboratory with the same technology or will it be done by a different laboratory with a completely different

technology? You know, we've already seen that precedence with array CGH analysis in confirmation of positive results.

DR. RANSOHOFF: I think the answer to this is, in general, the answer would be yes, but it's sort of hard to handle it in the abstract. And I would envision that as you review this on a case-by-case basis, if this is what you do along the lines of what Dr. Kondratovich outlined, that all of this is sort of going to come out in the wash and you're going to know about what threshold is important, and if you haven't crossed it for treatment or action, do you need to get another test? But it's sort of hard to handle in general. If you do it quantitatively, I think the answer is going to get clearer, and then I would suggest strongly considering that.

DR. MORIDANI: Can I have one more comment? And I do not know that this has to be done by reflex test or offered to the patients to seek.

DR. WATERSON: My question about the confirmatory testing, if the risk change is very small in either direction, are we going to be ordering a lot of unnecessary tests?

DR. WYNE: And what are we going to order as the confirmatory test? Does the person have the option to order their competitor's DTC or are they going to bring the report in to me and say, "You're my doctor. This says that I need a confirmatory test. Please order some test." I mean my gut reaction is absolutely. If something's positive for

a rare condition, you need to confirm it, but you can't just say get a confirmatory test. I think we need to -- there needs to be some more detail to the person of what to do, how to proceed.

DR. TSONGALIS: So I think the other issue that you're going to run into is that a lot of these genes are proprietary and the mutations are proprietary, and getting a confirmatory test from another laboratory is not going to be possible.

DR. WYNE: Well, that goes back to the genotype/phenotype correlation also, though. I mean, you bring it into me and I look up the gene and I say, well, there is no phenotype with this gene; what does it matter?

DR. SHAMBUREK: Bob Shamburek. I think one of the things is the FDA -- if that's part of labeling, it's sort of a package insert and it's something that if a test changed, it would have to come back to the FDA before you could change the labeling.

So, you know, I think the patients need to be informed, their need as a confirmatory, and in one sense -- and I don't know that the FDA could require that it's on the Internet, but we could also require that there are guidelines set up by established organizations. And I think in our reading material, we also heard that the NIH is establishing a genetic testing registry. That is a voluntary thing, but I think that could be one part of the solution. But I think it's a problem when you put something in a package insert as a requirement. I think there needs to be, but I think there needs to be input

for physicians to know where they can go and locate reliable information after the test.

DR. WATERSON: George.

DR. NETTO: George Netto. So in my opinion not only a confirmatory test is required and potentially by a different technology and source, but also the results should be highlighted that this specific test that you tested positive, this is a potential problem; the false positive rate is higher than the other test components, for example. So that needs to be very highlighted for the patient because, again, we're depending on that patient to follow up.

DR. LUBIN: So one issue I would like the FDA and others to be aware of is when you're talking about rare diseases, many times you're talking about a vulnerable population, and that's newborns, in which sometimes these tests are marketed to. So their use can have significant importance in how the results are -- the reliability of the results, how they're understood and the actions that are taken in addressing a condition, or may or may not be there. So I would urge the FDA to take that into consideration.

DR. GALLAGHER: I think that it's even more important as we look to the whole genome sequencing process and the additional variables that will be found there, that those kind of things take place.

DR. MANSFIELD: Okay. Thank you.

We'll proceed with the second part of the question. I'm going to repeat the first part: In testing general populations for rare conditions or markers, the false positive rate, otherwise the proportion of positive results that are false, can be significant. Should such tests be offered only to populations with higher prevalences of the condition or marker?

DR. WATERSON: No comments? Go ahead. Sorry.

DR. GALLAGHER: Colleen again. I think one of the issues we come back to is the whole concept of buyer beware. If it's direct-to-consumer process that we're talking about, the consumer bears the burden of what they choose to spend their money on and their time and their worry and all those other kinds of things. So I don't know how they would know in advance that they were someone of a higher prevalence for something. So I think it would be very difficult to do that kind of process.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: If we say yes to this, we get ourselves in a trap that would sort of contradict what we said above about being open and what have you.

DR. MAHOWALD: That's right.

DR. D'AGOSTINO: So, you know, I think I agree with the comment you just made. It would be very hard to define these populations kit by kit, study by study.

DR. MAHOWALD: Yeah.

DR. WYNE: Kittie Wyne. How are you going to control who purchases it? I mean, it's one thing to say we recommend this only be done by people of Afro-Caribbean descent, but the cashier at Wal-Mart is not going to say, sorry, you look Caucasian; so I can't sell this to you. I mean, how would you control target populations?

DR. WATERSON: I don't think from our first comments that we had meant to control population. We just meant to advise people.

DR. MAHOWALD: Well, we'd be inconsistent if we answered -- if we said that the test should be restricted in its offering here. We'd be inconsistent with what we seem to agree on in the second question under (a).

DR. WYNE: Yeah. If you're going to make it open to anyone who wants to buy it, then you can say, you know, this is the risk in target populations, but you can't say we recommend you not do it. And it's like we said, people don't know their ethnicity. I have a friend from India who turns out to have a CF gene. What's the prevalence of CF in India? You know, things like that.

DR. HIRSCHHORN: I would like to really support that, leaving it open. I can't tell a funny story here, but I would say that I know one which illustrates very clearly about finding on the basis of ethnicity, gene mutations that you would not have expected. And I think that's common experience of anyone who has done any sort of testing. I think it just should

be up to the person and just test people. It's not a big deal anymore.

Okay. Thank you.

DR. WATERSON: Okay.

DR. MANSFIELD: Thank you.

The next question, part (e), on number 2, harkens back a little bit to yesterday's discussion: Should medically actionable results for certain direct-to-consumer genetic tests always be routed through a clinician or specialist? And routed through has the same meaning as yesterday; that is, the result is delivered directly to the clinician or specialist and not the patient directly.

DR. WATERSON: George.

DR. NETTO: George Netto. So I do have a question. So how do we deal -- I mean, potentially, the reason the patient is ordering a DTC is he or she does not want this to be in their medical record. So how do we deal with this issue?

DR. RANSOHOFF: That got dealt with by the HIV test yesterday, didn't it? I mean there's precedent for that if people wanted to do it.

DR. WATERSON: Valerie.

DR. NG: Actually, I think we have a model for that. That's newborn screening, right? Those results go somewhere. I don't know where they go, but when they're abnormal, somebody tells me I need to do

another test on that baby, and that test goes off to some lab. So I think we already have a model to do this.

DR. WATERSON: That test result goes back to the medical record.

DR. NG: I've never seen them.

DR. WATERSON: But they do go back to the medical record.

DR. NETTO: Even the DTC?

DR. NG: No, we're talking the newborn screening.

DR. WATERSON: I'm talking about newborn screening. That result goes back to the medical record in the hospital, at least they do in California.

DR. MAHOWALD: I guess I'm surprised. I wouldn't think that the main reason for people doing DTC tests is that they don't want it in their medical record. I don't know. I'm sure people -- well, maybe. I don't know if people from the companies would be able to tell us that. I think there are other reasons. A lot of these tests would not be covered and a way through which a person can get the test is to buy it from a company if he or she can afford it. So I would think that that would be a more prevalent reason than I don't want it in my record.

DR. NETTO: No, I'm not saying it's not doable, but this is something that we need to, in the power of the consent, embed it in the consent, saying that if this is going to be positive, it's going to be reported to

your clinician and who's your clinician. So I'm just thinking.

DR. WATERSON: Bob.

DR. SHAMBUREK: Bob Shamburek. I think, I mean a lot of the practice of medicine is routed through the physician. We don't have direct-to-consumer pathology, direct-to-consumer radiology. Yes, the patient can get their information, but it's generally felt the interpretation is good. And in a sense, high risk genes such as Huntington's and others potentially could have an impact. We're still trying to find out the question of anxiety. To know you have a 12 percent increase in hypertension would be one where it would be less anxiety. But I think the FDA is going to have gauge -- if this test was perhaps a Class I, the potential might not be there that it could go directly to the consumer; the physician and the consumer could see the results. But I think for our guidance right now, the ones -- since it's hard to differentiate that directly back to the physician, if it's going to be a prescription one, is in general the best guidance.

DR. LUBIN: Ira Lubin. So just to clarify the newborn screening, newborn screening is a process -- it's not a single test -- that's run by states. And it's a screening test, so it's not a diagnostic test. And the result, when positive, is followed by the state. Results are reported to the physician, in which confirmatory testing is then ordered and a diagnosis is or isn't made. Screening simply places a patient in a population of higher probability of having the disorder. It typically doesn't make the diagnosis.

That said, some tests for rare diseases that are offered applicable to newborns don't have those controls and oversight in place. So if persons decide to use those tests essentially outside of the medical system, where there may be decisions made on whether to pursue or not pursue the results, at this point, you know, we can speculate but we really have no data, but there's the potential for harm considering the significance of some of the conditions that are offered for testing or may be offered for testing in the future.

DR. HIRSCHHORN: Rochelle Hirschhorn. I just would like to raise a question -- I don't know if this is the time to do it -- about the differences between states, particularly with respect to newborn screening. So, for example, California is one of the few states in which they keep the test papers. New York throws them out. But it raises other issues, and I don't know if this is not the time to do it, but the relationship of the FDA to state laws and rules, and this is particularly significant for New York State, and I don't know about other states.

DR. GUTIERREZ: I would say that this is not the place to bring that up.

DR. HIRSCHHORN: Okay.

DR. GUTIERREZ: I think the issues are quite different and so are probably not beneficial for this discussion.

DR. HIRSCHHORN: Okay.

DR. NG: This is just really quick. Valerie Ng. We've been dancing around privacy issues. Is somebody going to talk about privacy? Are we going to be asked that?

DR. MANSFIELD: No, you will not as far as I recall.

DR. TSONGALIS: So here's another issue I'd like to bring to the table. One is in the question it actually mentions medically actionable, and who determines that? And based on that, who will determine which physician it goes to?

So, for example, everybody in the audience is ready now to order a DTC on their cell phones and we'll have results this afternoon. Dr. Netto, everybody, is the local lab expert. Send all your results to him. So George will get these results from 80 or so people, 100 people, and look at them and he says, I have no idea what all these genes in this panel do. This is genetics. We'll send it to Ira, the local medical geneticist. Ira will look at these results and say, this is all nutrigenomics. I know nothing about this. Let's send it to the nutritionist. The nutritionist will say these aren't my patients, send it back to the primary care physician, and we'll go in a vicious circle.

So who decides where these results go? And in every one of those instances, you have potential HIPAA violations.

DR. WYNE: Kittie Wyne. I think the answer is in the original question and the original test is the clinical significance. And so if we have

genetic markers that don't have any clinical significance, meaning a direct action, a direct genotype/phenotype correlation, then is there a harm to allow it as a DTC? In other words, how about anything that's allowed as DTC isn't medically actionable. Do you see what I'm saying? I'm just turning the question around.

DR. GUTIERREZ: Let me see if I can help focus this question. I think the idea that these are DTCs, so a consumer orders this. The idea of the results not going directly back to the consumer, or at least to us seemed to be issues that we would consider if there was a particular disease or particular symptom that would require an intervention by a clinician, not just in general. So, you know, the idea of whether, you know, who owns the data and whether a clinician is involved or not, without the previous consent, or if -- well, it would have to be consented somehow by the person who orders it, but it would be in a limited case and in limited circumstances. So, for example, Huntington's disease may be one. You know, if there was a test for that in the panel and if it tested positive, would it immediately require that that kind of information be given back through a physician?

DR. WYNE: So how do you decide what's medically actionable? I mean, if you're going to have 100,000 genes on the chip, you're going to have to go through and screen every single one of them then. But if you require they show you the clinical significance for the test, then you can decide which ones go DTC and which don't.

DR. RANSOHOFF: That's what should be done.

DR. DAVIS: My question deals with the semantics of the question. You used the term "always routed." I just think that, you know, some careful consideration should be extended regarding possible exceptions so that when something is taken to its logical conclusion, you don't come up with unintended consequences. So the word always, as a lawyer, kind of bothers me.

MS. HOUSE: Hi, Tiffany House. Could it be just part of the process of ordering the test that in filling it out, the patient has to fill out their primary care doctor or whatever doctor information and say -- you know, have it explained to them that in case one of these tests comes back with a certain result, the information will be routed through your doctor; please provide your doctor's information?

DR. D'AGOSTINO: I hate to raise it again, but didn't we yesterday say some of these tests were of such importance that they should go through the doctor. I mean, are we now saying that if they make them direct-to-consumer, then there's some other rules being involved? I mean, I thought we were pretty clear on labeling the categories of tests that need physicians' involvement.

DR. HERSCH: Yeah, I think it should be clear that we are thinking on things that are high risk are probably not appropriate to not go through physicians.

DR. RANSOHOFF: But we're just advisory, and the FDA can make up their own mind and decide to not do that.

DR. HERSCH: Sure.

DR. RANSOHOFF: And so this is covering that contingency, I think.

DR. LEE: I would echo that. Basically our discussions yesterday suggested that we needed these checks and balances and that's why we want these tests done through healthcare providers. So I think it's actually difficult for us to advise on this particular question based on that.

DR. GUTIERREZ: I think that's fair. When we put these questions together, we have to think about the possibility of going either way. If the Panel had loved it, and everything should have gone over the counter, we would ask this question as -- you know, so I'm happy with moving on.

DR. WATERSON: Okay. Let's move on then.

DR. MANSFIELD: Moving on to part (f) of Question 2: What should be the involvement of a genetic counselor, if any, when ordering the test or providing direct-to-consumer genetic test results?

DR. WATERSON: Go ahead, Joann.

DR. BOUGHMAN: Fortunately or unfortunately, this is at least in part a medical practice question. I believe anytime we have used the term qualified health professional, I would suggest that a certified genetic

counselor would be among those, but actual practices and certifications, rights and responsibilities of different healthcare professionals will vary from state to state, so that one would have to be operating within the state laws as well as this. But I would feel very strongly that nurse geneticists, genetic counselors, boarded geneticists, there would not be questions about those people. I would actually have more questions about primary care physicians and general nurses than I would genetic counselors.

DR. MANSFIELD: May I make a clarification? Point taken. The clarification for the question is what should be the involvement, if any, of a person such as a genetic counselor?

DR. MAHOWALD: I noticed in all that we saw, it was always mentioned as a qualified counselor. I think that term is good, but I think some adjective there is crucial because I agree that there certainly are many clinicians who would not be as qualified, for example, as a certified genetic counselor in this role. And the companies, it seems to me, are therefore obligated, if we insist that they provide such counseling, to make sure that the person or persons who do that job are qualified.

DR. GALLAGHER: I certainly agree with Mary, but I also want to note the fact that there really aren't enough genetic counselors that are certified. I mean even hospitals that do a lot of genetic testing struggle to find the adequate number of qualified people who are certified to do this work. So I think we have to be careful with that.

The other thing that is -- you know, I'm an ethicist, so one of those issues is conflict of interest. Who do they work for? So if you're a genetic counselor and you are hired by the company doing their tests and counseling, you know, on their behalf, I think that's also a concern to me. At least normally when you have a genetic counselor hired by a hospital or something like that, a lot of times those genetic tests are sent off site and then counseled internally.

So I think there's some challenges that would have to be addressed into how that process would occur, but I think that genetic counselors who are certified and/or licensed in some capacity are probably the best people to be able to help people look at their results and understand what action they might take into the future.

DR. WATERSON: Is the question asking, should they be required to be involved in the process or should they be available to be involved in the process?

DR. MANSFIELD: That is what you may recommend to us.

DR. WATERSON: Bob.

DR. SHAMBUREK: Bob Shamburek. Because I'm kind of hearing the interpretation as the involvement of genetic counseling, not specifically on the accreditation or all that. You can have subspecialty organizations, a cardiologist who makes recommendations and they're not a genetic counselor. But I think it's more of -- where I see it is, if you can have

an expert who's in Huntington's, that is great; otherwise, someone with genetic expertise probably should be making that information. But I think what is the whole new wave, is with all these whole genomic and whole exome, where you're making vast screening, that almost would overwhelm a subspecialist; it would overwhelm a family physician, where someone with expertise in genetic counseling to know that would be more important in advising that person.

DR. WATERSON: David.

DR. RANSOHOFF: I think if we think that something is so complicated that a genetic counselor needs to be involved, then maybe by definition it shouldn't be DTC. And what I'm thinking of is in screening 40 and 50 years ago, many people got screened for diseases where there was no counseling and follow-up. They just didn't have them. And one of the criteria of the task force early on was if you don't have the resources really available, then you shouldn't be doing screening because that can cause mischief and problems. And if we think genetic counseling is really necessary, then perhaps that ought to be something that is initiated so that there's contact before the information even comes through and that's at least a consideration.

DR. WATERSON: Ira.

DR. LUBIN: So there is precedent for a recommendation for including -- I'll use the language, counseling by a competent individual in

several, I believe, guidances that have been made. Certainly when we were involved with the OECD, we considered that issue very carefully and, you know, that's a principle that we integrated into that document. And I believe that I've seen that in similar discussions and guidances, although I would have to go back and look to confirm when this issue was considered before within the U.S., the idea being that the recognition that DTC for genetic testing is complex, but if you're going to go that route, genetic counseling should at least be made available to help the individual understand and act on their results appropriately.

DR. WYNE: Kittie Wyne. I would suggest that we should recommend the involvement of a genetic counselor, and the fact that there's not sufficient numbers at this time is not a surprise because this is a whole new growing field, and there will be more people and more people will be trained and especially as there's a need for it, but people do need assistance in understanding the information that's available to them. And so if we're going to allow these to be DTC and without the requirement to speak to a healthcare provider, at least the genetic counselor is giving them an option to understand it. Remember, right now what we saw yesterday is, what, only 10 percent actually talk to the counselor. Hopefully that will grow over time, but it's only going to happen if the person's available. And if we request that it be available, then it makes it more likely they will speak with that person.

DR. WATERSON: George.

DR. NETTO: Yeah, I fully agree with that, and it has to be somewhat -- again, we're not talking about an umbrella to hold the whole gambit of testing. So depending on the sophistication of the interpretation, that should be a must.

DR. SHAMBUREK: Bob Shamburek. I'd like to just say one other thing. We have to be very careful with the wording because even though cost is not an issue, the majority of these tests are not going to be reimbursed, and neither will a visit to a genetic counselor. So that's not an issue but that could doom a majority of these tests, and I think we do want to see them available if there's competent genetic counseling available.

DR. MORIDANI: I also agree. I think it's important that genetics counseling be available and we should not really worry about the shortage of genetics counselors because, truly, we do not know how DTC market, how big is the market. So it might not really fly.

DR. GUTIERREZ: David.

DR. RANSOHOFF: David Ransohoff. I think we might be inviting mischief if we ask people to get testing of certain kinds of things and say you ought to talk to a genetic counselor but don't really have that in place. When hypertension screening was started in the '60s and '70s -- and this is really simple and people can understand it -- 50 percent of people who had high blood pressure didn't go to doctors afterwards. Here the

number would probably be even higher because it's hard to find genetic counselors.

Furthermore, there was mischief caused -- when people got labeled with hypertension, even if it was mild, the study that David Sackett did in the *New England Journal* showed there was absenteeism from work. No one ever expected that this kind of thing would happen. We don't know if that kind of thing is going to happen here, but I think we're just inviting problems if we tell people, get tested, and then it's your job -- we think that you ought to see a genetic counselor, but we're not going to have any of that in place to begin with. I think we've got experience with diseases where that's caused mischief, and we at least ought to keep that in mind.

DR. WYNE: But the companies do have that in place already. We heard about that yesterday, at least so far.

DR. RANSOHOFF: If it's routinely in place and offers enough information, but we've also heard that people may punt and, you know, send people back to Ira and this person and that person. I mean, if something's in place, then maybe that can work, but I think it's disingenuous if we leave too much in the hands of the person and if there's not something in place. So that at least ought to be considered.

DR. WYNE: No, I agree, but the model we have already does show that it can be done but still the patient using the resource is the problem.

DR. RANSOHOFF: Okay. If that works.

DR. TSONGALIS: I think one of the questions I'd like to put out there is that either I'm confused or maybe we're confusing the issue between genetic counseling and clinical counseling -- you know, there's an overlap -- and who will do what. And I don't know that a genetic counselor is the best person to do clinical counseling, but neither do I believe that a healthcare provider physician or nurse is the best person to do genetic counseling, and so I think we have to separate those two entities.

DR. WATERSON: Anybody? Go ahead, Steve.

DR. LIPKIN: This is certainly an evolving field. For example, there programs specifically to train oncologists, you know, who have an interest in genetic counseling and genetic management of patients who have genetic susceptibility gene mutations, you know, that's a target population. So I think it's sort of wrong to just say they have to see a genetic counselor. But my view as a board-certified geneticist is that they should have to see a qualified health professional, but that will evolve and is evolving constantly over time. That certainly includes genetic counselors.

DR. WATERSON: Maybe the availability of genetic counseling should at least be a minimum criteria?

DR. LIPKIN: Yeah, perhaps the involvement of genetic counseling by a qualified individual and not necessarily leave so much as to whether that will end up being genetic nurses, genetic counselors,

geneticists or other qualified individuals.

DR. WATERSON: Do we need any more comment on this or are you happy?

DR. GUTIERREZ: I think we're happy. I think we can --

DR. WATERSON: Okay.

DR. MANSFIELD: Okay. The next question will enter into a little bit of what was discussed today regarding tests that report risk. Many companies currently marketing direct-to-consumer genetic tests report genetic test results for risk as relative measures, such as relative risk, odds ratios and so on, based on currently available publications. The way in which risk information is communicated may affect the individual's perception of the magnitude of that risk. Are some measures of risk more easily understood by consumers, for example, relative risk, absolute risk, or descriptive categories such as low, average, or high risk?

DR. WATERSON: David.

DR. RANSOHOFF: Relative risk is almost outlawed now by the major journals. If you present relative risk without discussing the absolute risk, you can't get into the top journals, and there's a reason for that and it's because doctors, patients, decision analysts, anybody who is really serious, can't understand if you don't have some kind of anchor. And especially if we're going to be talking to normal human beings and consumers, it has to be presented very clearly in terms that they understand.

DR. D'AGOSTINO: This is one of those questions that maybe the discussion is more useful than trying to get an answer down, but I agree wholeheartedly with what was just said. With some of the guideline panels in the cardiovascular field, the absolute risk is the way one decides on treatments and those are oftentimes based on economic evaluations and what have you. And I mentioned a while ago that with the adult treatment panel for cholesterol, the cutoff of 20 percent for the developing of coronary disease within the next 10 years was basically the probability of somebody already had a heart attack or developing another heart attack, so there's something they could pin to that. And so absolute risk does have an appeal to it.

One of the difficulties that we have in the cardiovascular field is if you tell a young female that she has a 2 percent chance of developing something in the next 10 years, but you have high lipids, she may be more attracted to the 2 percent than she is to the blood pressure or the high lipids, and so relative risks do have a place. And we've tried games like vascular age and heart age, to say you have a 2 percent risk, but you have -- you're 25 years old, but your heart and your vascular age is more like a 40-year-old individual. So you have different audiences that you have to address these things to and I think that it's pretty hard to say you should always do absolute risk and relative risks don't have a place. But I would support the idea that you have absolute risks, then you have a different

audience where you may have to -- or a particular audience where you may have to buttress that with what the relative risk means, and you can then look at low, mid, and high risks by looking at the absolute risk in making some sensible cutoff points.

And there's also, just lastly, there's the short-term risk versus long-term risk. If you go into one of the questions that's down -- the next one, where you add other variables, you can start talking about your risk is a 10-year risk, but if you're not a young person, your risk 30 years down the road or your lifetime risk, and there are a lot of different ways of presenting these. The point is to get the message across without being deceptive but to get the message across. And I think, again, supporting the absolute risk is the start point, but there are a lot of variations, supportive information that might be needed that give the user more understanding of what is actually before them.

DR. LEE: If I go back to the question here and it says what's most easily understood by the consumers, I guess for me I would say the descriptive categories would probably be the most easiest to understand, but it would be helpful to have that associated with a number rather than just description. So there would factor in, I think -- the next easiest thing to understand for me would be the absolute risk, but again that's -- you know, as a consumer, that's probably my recommendation.

DR. WATERSON: Steve.

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DR. LIPKIN: So I've actually seen patients who have had some of these, you know, sort of association type tests we've heard about from companies that have presented. So I'm reminded of an individual who came actually to see me who was interested because he had tested positive for covariates that affected his risk of Crohn's disease. So the bottom line is that, you know, in this individual, I think there was a lot of confusion over absolute versus relative risk. And my experience actually with this individual and many others is that really absolute risk is really what the patients tend to understand the best, and I would advocate just in my own personal experiences with these activities, that absolute risk be very prominently displayed, and if we want to have relative risk and other things as well, that's great, but I think it's most important. So this individual, for example, felt that he was at very high risk even though he had no family history, had no active symptoms and such. So absolute risk, to me, in my experience, is the most important.

DR. RANSOHOFF: David Ransohoff. Again, while we can't resolve it here, I think that it would be very fair for you to require of sponsors some appropriate consideration of how they communicate risk. And there's a very big risk communication field and also there's a course that the NIH runs for media about reporting risk in medical articles that Barry Kramer runs, that would have lots of literature on and I think you could defer to sponsors. But, in general, this is a really, really important kind of

issue to make clear to patients.

DR. D'AGOSTINO: Just to go back to something we mentioned earlier, you may have the analysis done on a particular population. As you move into a different population, the absolute risk may change, but the relative risk may tend to be more stable. So you have those considerations also in terms of what's the way to convey this information.

DR. WATERSON: Okay. All right. The last part of the question.

DR. MANSFIELD: The last part of the question has already been touched on a small amount. Should test reports for direct-to-consumer genetic test reporting risk for future disease include warnings or information about additional factors beyond the reported genetic markers that may refine the individual's specific risk, and by this we mean other variables such as environmental and other health status?

DR. WATERSON: Ralph.

DR. D'AGOSTINO: I don't think you need anything else. Just forget about it. Just go with the medical. Obviously I've been arguing for a day and a half that I think that you really need to build those other factors in, and I was arguing -- and again how one conveys that in terms of regulations is not something I know, but I think that the assessment tools should build that in, that you shouldn't give a probability and then say, you know, this probability may change depending on your family history and so forth, but somehow rather the kit should have state of the art in it, and that

would be my suggestion.

DR. WATERSON: David.

DR. RANSOHOFF: David Ransohoff. I think this is a fascinating question which really helps focus the issues because when you look at the in vitro home tests that we heard about earlier, you don't need to know all this other extenuating circumstance stuff for an HIV test or for a pregnancy test. But what we're really asking people here and Ralph's been talking about for the last few days, this is the practice of medicine, and this is the interpretation of all the complexity. And what we're really asking the sponsor to do, if they want to do this, and they may want to do this, is to get into all this other complexity when what they really want to do is to sell and provide a test, and the other complexity may be important, but it's not sort of their main goal. It's inherently complicated. It could be doable, but I think there's a real contrast here between the things that are simple and the things that really aren't simple, and the patient is really not interested in what's my test result. What they're really interest in, whether they can articulate it or not, is what's my risk that this test result purports to tell me about? But all these other extenuating things may be important, and that's the kind of complexity that makes this different from the current home in vitro things. It's much closer to the practice of medicine which any one particular product really doesn't do.

DR. NETTO: George Netto. So to frame it in another way, this

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is the mitigating tool that's going to bring a lot of the DTC back to prescription testing because in order to do it properly in a way that you're really truthfully integrating all the additional information -- maybe for certain things there are mathematical tools that they can build like Ralph was saying, but for a lot of these there isn't. So potentially for cardiovascular, for Gail's model, so that could potentially be doable, but for the majority, it's not going to be doable, and that's going to be the reason why most of us are feeling a lot of these tests are not going to end up being safe enough to be in DTC.

DR. WATERSON: Ira.

DR. LUBIN: So if I order a test or if someone orders a test and provides the company complete and accurate input data, then, you know, I would say that there may not be a need to really extensively consider this issue. I would say that that's probably not something that you will have assurance that will happen. It doesn't happen in clinical laboratories that are well established and have good rapport with clinicians.

So with respect to that, and we know from some of the talks yesterday and broader knowledge, and just the lack of, you know, our scientific knowledge in general, that we're not going to have in many instances that kind of input data where we can always produce a result that is accurate and reproducible in that respect.

So with that, I think it's necessary that one does provide

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warnings or information about additional factors that might modify the interpretation of the test, and furthermore, if this test result is taken to a physician, the physician may want to know more information, other than there is a low, medium, or high risk for whatever the test is measuring.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: Just to go back, the point that I'm trying to make is that when they develop these, what the consumer actually uses is one thing, but when they develop these, they should be done in light of the existing knowledge that you can't just pull out genes for diabetes without telling individuals that there's a whole set of clinical parameters -- not a whole set, a small set of clinical parameters that would pin your diabetes, type 2 diabetes risk very well, and these genetic factors aren't necessarily going to help and so forth. It's this how do you present to the individual a probability or a risk that isn't in some sense deceptive and isn't -- well, it isn't deceptive or it may be deceptive if you're not presenting and you're not developing these kits with that knowledge, just to go blindly developing them.

Again that's not to say how you present them, but to develop them and to present them to the FDA, does this factor make a difference? I can't imagine that you would develop kits and present them to the FDA for approval and the -- says you don't need this because -- or you should have done some kind of a net reclassification analysis in order to find out if you're

going to gain any information from that; what more information are you getting from this than clinical parameters? And I think that should be presented when it goes to the FDA. Again, how you package this to the consumer is still a different issue.

DR. WATERSON: Steve.

DR. HERSCH: I think I'm -- yeah, I wanted to say something very similar, which is basically this is a -- the packaging or the labeling implications for this are really important in that essentially it needs to be gotten across in multiple ways and everywhere possible that the medical value of this test is uncertain, and your true risk of whatever disease is associated with the finding has to be considered in the context of many other risks, many of which may be much more important in determining your true risk, and, you know, this may be best understood with your healthcare provider. I mean that's going to have to get stamped all over everything, and with return results and marketing and -- you know, it kind of obviates the value in some way.

MS. HOUSE: Hi, Tiffany House. I guess I'm just kind of thinking back through the bigger picture and process of what we're talking about here. If we go with the hypothetical that there is a test that passes all of the validity and it meets that criteria and standard that the FDA sets, then the next question is, in my opinion, how is it going to get to the patient? And I mean, I think that if there's a test that in and of itself may or may not have

super great information standing alone, but may be somewhat useful, why wouldn't you tell a patient, okay, this may not tell you everything you want to know; there's probably other factors that need to be considered and these are what they are, and let them do with it and have that full and complete knowledge. I don't think that necessarily we should say forget the test altogether because they're not taking everything else into consideration. Just give them, here's what you're getting.

DR. RANSOHOFF: David Ransohoff. I think a key mitigating thing here is what Tiffany sort of touched on and it has to do with risk. And you're hearing from us that there's a lot of complexity here, and there is, but that may not make that much of a difference, or you can say customer beware, caveat emptor, if there's not a high degree of risk of something coming from misinterpretation or not going to a provider, and that can be one key thing that can perhaps guide you in this.

DR. NG: I had joked at the break. Perhaps what we really need is an online pre-test and post-test calculator for those models that we know what are important factors for diabetes. What's your BMI? What's your age? If you had a lab result. Then you get a genetic test that tells you what your two outcomes would be and you can decide do I want to buy the test.

DR. WATERSON: Bob.

DR. SHAMBUREK: Bob Shamburek. I think we're really talking

about yesterday's discussion with the pre-symptomatic and the susceptibility because very much -- we've heard about the Framingham risk score. Well, if you're a smoker or nonsmoker, that's going to change your risk regardless of what your genes are. Dietary things will have that. You can't change whether you're male or female, but those things will all change the array, the information you get back, and that's where the input of the pre-test or allowing the person to know -- because you can't be assured that, okay, my genes are okay, now you can go out and smoke and things. So that information, I think, needs to be one of those limitations to improve safety, which will mitigate the potential of misinformation, I think.

DR. WATERSON: Okay. We need any more comment? Mary.

DR. MAHOWALD: I was talking to a few people at the break, and as long as we're on the subject of labeling, I want to make a really strong pitch and see how many other people would be interested in changing that term consumer to customer. I really believe it more clearly represents what's being offered from the companies and, you know, if we want to have truth in advertising, that really is the truth.

So, Mr. Chairman, would you like to ask how many people agree with that suggestion that the label DTC be translated as direct-to-customer rather than direct-to-consumer?

DR. RANSOHOFF: Why, Mary, does that make a lot of difference? What's the key idea?

DR. MAHOWALD: The key idea is that people are buying these tests for themselves.

DR. WATERSON: Or for others. Is that what you mean?

DR. MAHOWALD: For companies whose main goal in offering these tests is their own profit.

DR. WYNE: So what's a consumer?

DR. RANSOHOFF: So people be more cautious or they'd be more alert if they saw themselves that way?

DR. MAHOWALD: Many of these tests, since they're not prescription, prescribed tests, are not going to be covered by insurance because in many cases they're not crucial to the provision of health. I mean, we heard -- as a matter of fact, one of our speakers yesterday talked about his wanting to have his whole genome tested because he just wanted to know his whole genome, and I just really think that the commercial aspect of offering tests by a company is just much more clearly expressed by using that term.

DR. WATERSON: I don't know if we can make that distinction. I see what you're trying to say. I don't know if that's going to help the people that are going to use the test all that much but maybe it would. I would say probably not. Are there any other comments?

DR. WYNE: I'm confused then. So I just looked up these words. The difference is purchases versus utilizes. That's the semantic

difference. So you're just trying to emphasize the fact that --

DR. WATERSON: We would assume that the purchaser is going to be the user --

DR. WYNE: Yeah.

DR. WATERSON: -- but that may not always be true.

DR. MAHOWALD: That may not always be true.

DR. MANSFIELD: May I make a clarification that this is the language that we have used for simplification, direct-to-consumer. These tests are also called direct access and several other names. This is our simplification. It is not necessarily how the companies advertise themselves.

DR. WATERSON: Are there any other comments?

Why don't we break for lunch? I just want to remind everybody not to discuss the -- okay. We'll now break for lunch. Panel members, please don't discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene at 1:00 p.m.

(Whereupon, at 11:48 a.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:00 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 relevant 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 financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this 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. Each speaker has been given 10 minutes to present. When you begin, the green light will appear. A yellow light will appear when you have one minute remaining, and at the end of the 10 minutes, a red light will appear and the microphone will actually turn off. Since we have nine speakers today, it is very important to adhere to this rule.

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 any questions.

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

DR. WATERSON: The first speaker will be Dr. Adele Schneider.

DR. SCHNEIDER: Thank you very much for the opportunity to address this distinguished group. I am employed by the Victor Center, who is paying for my travel expenses. I don't know if that's relevant.

The Victor Center for the Prevention of Jewish Genetic Diseases is an organization within the genetics division in a hospital in

Philadelphia. And we provide education, counseling, and carrier screening for 18 diseases that are more common in the Ashkenazi population, and we do this with community and college screenings, and we use this medical model where we ourselves go out and do the screening. Everything we do is with genetic counseling and informed consent.

Our major concerns with direct-to-consumer testing really concern primarily Tay-Sachs disease. We feel that with the direct-to-consumer testing, where there is no informed consent, without genetic counseling and no medical professional involved, information may not reach all family members if there are carriers identified. And also the testing process, they will not understand that there is residual risks and exactly what is being done.

Another thing that we're also encountering is as the panel increases, we get people calling us for their results from prior testing because they want to be updated, and if you don't have a medical repository for that information, they don't know where to turn for that information, and then I'm able to speak to them or the genetic counselor, to give them more information about what they need to do.

To be specific about Tay-Sachs, for just a brief moment, Tay-Sachs enzyme, the hexosaminidase A enzyme is what is deficient in Tay-Sachs disease, which is a neurodegenerative disease. Babies are born looking fine, and within 4 to 6 months, they start to lose skills and they

usually die about the age of 5 or 6.

In the 1970s, the enzyme was identified and an economical test became available and population screening began in the Jewish community, with the community buying a lot of education, and based on that, the incidence of Tay-Sachs in the Jewish community dropped by 90 percent.

Today there's DNA testing available with a variable number of mutations in each lab which would alter the sensitivity a little bit. The best test sensitivity for Tay-Sachs disease is enzyme and DNA together.

There are several methods to identify the HEXA levels. Serum is what is standard in most labs, but it has a high inconclusive rate. Leukocytes are the next best and you can do that in pregnant women because the serum is affected by birth control, pregnancy and diabetes. But the best is the platelet HEXA level, which has a very low inconclusive rate. It's the most reliable and least available.

Just briefly, we did a study of over 1,000 students who we screened. We did Tay-Sachs platelet enzyme and DNA, and we identified 11.4 individuals in that cohort who were positive on Tay-Sachs enzyme and negative on DNA, 1 of whom was sequenced and we found a novel mutation, and all had at least one parent born non-Jewish, which I think is the critical part of what we're trying to do here. When you have people going for direct-to-consumer testing, there is nobody really helping them identify who

they are and what is the right testing for them.

The Ashkenazi Jewish population, which is really our focus, is changing a lot. Demographics is different. It's not homogenous anymore because of intermarriage and adoption, and we feel very strongly you cannot rely on DNA only. When you do the direct-to-consumer testing with saliva or buccals, they're only doing DNA. So they're missing 11.4 percent of carriers. The ACMG guidelines consider 90 percent to be the state of a good test, that's a reliable test, if you were to take 90 percent. So our main concern is that enzyme needs to be done for Tay-Sachs to be done the right way.

In a non-Jewish person, and Tay-Sachs occurs in the general population in the Irish Canadian and French Canadian, Amish and other communities, the only way to do Tay-Sachs testing really is enzyme. The mutations for the Ashkenazi panel would not be useful to anybody.

So buccal and spit tests don't work. So the problem for us is people think that they've been screened for Tay-Sachs disease if they have a buccal or spit test done. This is a severe preventable disease, and if testing is not done the right way, the number of babies born with this disease will increase.

I think I'm going to stop there because I know you had a lot of discussion yesterday, and I think I'm just going to be reiterating a lot of what you already talked about. Thank you.

DR. WATERSON: Thank you very much. We'll proceed with

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our second speaker, is Destry Sulkes.

DR. SULKES: Hello, folks. I'm very honored to be here as well. It's a great group of people we have. My views and statements, as you see here expressed for informational purposes, do not necessarily reflect those of my company, Medivo, nor the Alliance for Continuing Medical Education.

So we're here today obviously to talk about the issues surrounding direct-to-consumer testing, and I'm a physician and a co-founder of the medical virtual office, Medivo is the company. I'm also a volunteer board director and the treasurer for the Alliance for Continuing Medical Education, and that's an alliance set up with a mission of improving the healthcare of Americans.

The slides that you see and my statements are based purely on my daily interaction with patients and clinicians as a physician and as a principal of Medivo. I'd like to share some data that we've collected and surveys to gather clinicians' perspectives on the risks and benefits associated with making genetic tests with medical claims available for direct access by a consumer without a clinician ordering the lab test and overseeing the delivery of those results.

Since 2001, our company has addressed the unmet medical needs of those who do not have access to clinicians who have managed lab test ordering and lab test result delivery to monitor their health. We provide that access through our nationwide network of physicians who

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conduct lab test oversight safely and securely over an online platform connected directly to the major U.S. laboratories.

For genetic lab tests in particular, we require that our clinicians complete education programs modeled on those offered by the Centers for Disease Control and the National Institutes for Health, as well as validate their genetics communication competency as defined by the National Coalition for Health Professional Education in Genetics.

I'd like to reinforce last year's statement that we made at the FDA hearing on LDTs, where we think there's still a lot of confusion around the terminology and that's not helping advance the situation.

So, first, the term direct-to-consumer, or DTC, as you all know, was used in 1997 by FDA to describe a method of advertising that provides valuable product information and increases consumer awareness, but not for consumers to bypass their physician to obtain a prescription medication or a device whose use is restricted to medical professionals.

In contrast, there is a term called direct access testing, which is defined at the state level and describes a process wherein states legislate certain legislation to allow individuals to order a limited set of the safest and most well-established lab tests from CLIA-approved labs which analyze patient specimens and without a request nor a requirement for a physician's order or oversight.

Last, individuals can also purchase certain lab tests in a retail

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setting when approved by the FDA specifically and used at home, like pregnancy tests or glucose meters. These tests are called over-the-counter, or OTC.

To better understand how practicing physicians view the prospect of consumers ordering their own genetic tests and hear directly how they would prefer to have appropriate genetic tests ordered for patients in their practices, we collected survey responses from about 150 practicing primary care physicians. The surveys solicited the practicing physicians' views on consumer ordering for different categories of tests as well as their preferences on how genetic tests should be integrated into their medical practice. The surveys were not validated instruments and had not been used previously.

The relevant findings include: on this first slide, all respondents that we surveyed felt that there should be some level of restriction placed on consumers' ability to order genetic tests. Fifty-five percent felt consumers shouldn't be able to order the test directly at all, but 45 percent felt they should be able to order the test with some type of mandatory clinical support or clinical counseling provided.

Next, of the three types of tests the FDA described in the agenda for this meeting, we queried the physicians and we found that, indeed, physicians felt that different levels of risk led to different levels of restriction that should be applied. So from highest to lowest risks, the

physician respondents mentioned drug response as the highest risk, 80 percent that would restrict consumer ordering; disease risk 60 percent and carrier screening 40 percent.

About 25 percent of the physicians feel consumers would be likely to understand genetic test results and have improved healthcare outcomes, whereas 75 percent of physicians felt consumers would misunderstand their results and be unclear as to what actions to take next. And of that 75 percent, about 2/3 were worried that a consumers' health could actually be harmed if they were to misunderstand the results and take the wrong action, for example, if they stopped taking a prescribed medication. About 1/3 felt consumers would be likely to misunderstand the results but suffer no harm.

When asked how they'd feel about a fellow physician with specific genomics training and certification ordering a test for their patients and being available for clinical decision support on the results, about 80 percent felt this would be a positive impact on their patients' health, about 20 percent were neutral, and none thought it would have a negative impact. And all the surveyed physicians are accustomed to tests being ordered on their patients by other clinicians in their peer group and keeping the results on file for future reference.

Only about 40 percent of the physicians that we surveyed were aware of FDA's genetic test label changes for warfarin and clopidogrel

specifically, and only 7 percent are currently ordering genetic drug response testing in their practices. We think this is a pretty low number based on how important these safety information are that are in the labels.

And so to conclude, I want to share a clinical scenario. This is what our days are all about. So one of my colleagues, a female physician and primary care doc, one of her patients, who we'll call Joe, was a 55-year-old man, had his genome tested as a birthday gift from his wife, and it turned out that he had been taking Coumadin for over a year for his atrial fibrillation. His genetic test report, first of all, had a result on warfarin, and second of all, it said he was resistant. This made him very concerned. He told his wife he should probably just stop taking the drug, and his wife convinced him instead to call my friend, the primary care physician, and ask her if he should stop taking his warfarin. She, of course, convinced him the report didn't need urgent action, that she would like to see the report herself, to keep on taking his Coumadin, and to keep up with his monthly INR testing to make sure he was in therapeutic range.

So in closing, we agree that there are certainly different levels of risks on these tests, and given the results of our survey around clinicians' views on the risks and benefits, we encourage the development of further guidance and clarity on the regulations of the test and look forward to physicians continuing to be involved in the ordering and communicating the results of these tests. Thank you very much.

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DR. WATERSON: Thank you. Next is Mary Pendergast.

MS. PENDERGAST: Good afternoon. My name is Mary Pendergast. I am a lawyer by training. I spent 18 years at the Food and Drug Administration, the first 11 as a lawyer, the last 7 as the deputy commissioner of the Agency.

Since that time, I've been a lawyer in public practice where I represent a wide variety of companies. I'm on the board of directors of SRX. We are attempting to find a treatment for sickle cell disease, the first disease known to be caused by a genetic defect. I also have given advice to 23andMe and a wide variety of pharmaceutical companies that are doing genetic testing of each and every one of the subjects in their clinical trials in the hopes of advancing personalized medicine. But my views today are my own and no one has paid for my time or travel.

I've got to start out by saying that I think that this Panel has not been well served by this Committee hearing. You started your deliberations yesterday before you had a chance to hear the wonderful presentations by the three FDA employees this morning, and you did not have a chance to hear all of the people that are presenting.

Second, there were no company persons or enthusiasts for direct-to-consumer genetic testing invited to speak. So the 30-minute slots were reserved for people who are against it. The 10-minute slots are reserved for people who are supportive.

You also did not receive a balanced view of the data. Yes, you did receive information about a couple of trials that show that there is no anxiety when people get their genetic test results. There's a lot more trials. No one did a synthesis for you. But the bottom line from actual studies, as opposed to anecdotes, is that when people attempt to learn something they are not upset by what they learn even if the news is bad. And I think you should relate that to your own lives. Everyone's life has trials and tribulations. We can handle it.

Finally, the FDA mentioned the GAO report about the mistakes made by direct-to-consumer genetic testing. There's a couple of problems with relying on that report. First of all, the GAO did not mention that in all the direct-to-consumer genetic testing companies surveyed, the concordance on the actual analytical validity was 100 percent. Every A, C, T, and G was identical.

Second, the GAO said that some of the results were false or misleading or confusing. That's because the GAO lied. When the GAO sent in the spit to the companies, they sent it in once telling the truth, in other words, that I would be a white female, and the second time they sent it in saying that I was like a black male. They got different results. You heard from the FDA why that would be true. But rather than acknowledging their lies, they said the companies were giving misleading information. And I would like to say that the person in charge of that report was fired today.

My second point is that, and I regret to say this, you as a Panel are operating exactly according to type. The medical profession has objected every time the government has attempted to give direct-to-consumer information. The medical profession fought against women learning about their pregnancy at home. You fought when people were given the right to get HbA1c tests at home. You fought when the Agency proposed to give people the right to have HIV testing at home, and now you're doing the same thing. I mean are we surprised? I don't think so.

The criticisms and all of those other examples mirror exactly what you have been saying for the last day and a half: We won't understand; we'll do stupid things; we won't do the right thing. But guess what? Two points. One, that's not quite so true. There haven't been major problems or indeed any problems that I know of about pregnancy tests or HIV tests. And, secondly, it is frankly medical paternalism, the willingness of the medical profession to keep information from people for their own good.

I think also there's a problem of economics here. There's a lot of talk about how the direct-to-consumer companies will make money. Well, guess what? If we stick to your recommendation, that people go to you twice, first to get the prescription and then to come back and get the results, you get money twice. If we make the rule that not DTC companies can do this testing, your laboratories will be paid for the testing. So let's just sort of think about what we're saying here.

The other point about that is that you are not holding the direct-to-consumer companies to the same standards that you hold yourselves. The professional laboratories are fighting any effort by the Food and Drug Administration to require laboratory-developed tests to be subjected to FDA analytical validity pre-approval. You don't want that. You don't want that. But we all want that for DTC testing. If FDA regulates DTC testing, their analytical validity will in all likelihood be better than that that is going to doctors.

My third point is about governmental paternalism. The Medical Device Amendments were passed in 1976. But FDA doesn't just implement the Food and Drug Act, it has to implement all of the laws in this country. And since the time that 1976 law was passed, the Supreme Court has ruled in numerous cases that when the government seeks to restrict the information provided to a consumer, to a citizen, that it has to take the position that the information itself is not risky. The Supreme Court, when restricting the State of Virginia's attempt to restrict what information pharmacists could tell people, it said, there is, of course, an alternative to this highly paternalistic approach. That alternative is to assume that this information is not in itself harmful. The people will perceive their own best interests if only they are well enough informed and that the best means to that end is to open the channels of communication rather than to close them.

I think you had a fruitful discussion about all the things you could do to eliminate misconfusion. There's nothing wrong with disclaimers. There's nothing wrong with saying this tells only part of the story. There's nothing wrong with saying this is only your genetic information, your environmental factors are far more consequential. But that is opening the channels of communication, not shutting the information out altogether.

There are a few questions that have come up: Can someone be allowed to know anything when everything is not known? This has come up often. You can't possibly tell us anything because we don't really understand the full impact of smoking on heart disease, let's say. Well, the answer is yes. We can't live our lives where we can't know anything until everything is known. You're all scientists. You know that you never know everything, and if that standard was held to be the case, nothing would be told to anyone about anything.

Second question is can disclosures or limitations be used to explain things? Yes, absolutely. You answered your own questions a million times over the last day and a half about, we can't tell them this because they need to know that. Well, the solution to that is tell them this but also tell them that. That is entirely what FDA can require.

Another question asked is can you demand actual clinical improvement before the information is provided? The FDA has asked and answered that question no. You get your HIV test in the privacy of your

home, you are not compelled to go to a doctor. You are not compelled to take antiretrovirals. You are not compelled to do anything. You may die soon or long after that, but you are not compelled. When you get a pregnancy test, you are not compelled to get prenatal vitamins. You are not compelled to go to the doctor's office. That is beyond the scope of the government's control over consumers. So I would reject that.

I also think you don't want to be held to the standards you're imposing. You said, well, we need to have better clinical outcomes or we can't do this at all. Well, doctors don't do such a great job explaining to their patients why they need to take their meds.

In a recent study announced last month, 28 percent of all the prescriptions given to insured people were never filled. They were never taken to the pharmacy. Does that mean you guys are doing a bad job? I wouldn't think that that would be the case. I wouldn't think we should then say, well, don't let doctors do prescriptions; they're not very good at it.

Finally, there's ways around restriction. It is easy to divide these tests into two parts: one part do the genetic testing; one part give the information. If that happens, there's no intended use; there's no FDA authority.

So if you regulate with too heavy a hand, that's precisely what's going to happen. And I ask, is that better than having a system where accurate and non-misleading information is given to consumers?

Thank you very much.

DR. WATERSON: Thank you.

(Applause.)

DR. WATERSON: Our next speaker is Diana Zuckerman.

DR. ZUCKERMAN: Thank you. I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families and our Cancer Prevention and Treatment Fund. Our center focuses on improving policies and programs to improve the health and safety of adults and children. We don't accept money from companies that make medical products, and I have no conflicts of interest, and I'm not a lawyer.

My perspective is a little different than Mary's. I'm here as a scientist with post-doctoral training in epidemiology and public health, and I've dedicated my career and my work to improving healthcare for adults and children. I'm also a fellow at the Center for Bioethics at the University of Pennsylvania.

And as head of a nonprofit organization that provides information where we basically explain complicated medical information to consumers, to health professionals, to the media, and to policy makers and opinion leaders, and we do that for free, so I spend a lot of time, and we spend a lot of time trying to explain complicated information. And for that reason, I think our perspective on the topic of the day is a little different, and I'll try to share that and my perspective in epidemiology and public

health.

So, first of all, I agree with the view that these products need to be carefully regulated, and I think that testing and diagnostic testing, genetic testing and other kinds need to be carefully regulated, whether the person getting the information is a physician or some other clinician or a consumer.

And, a very important part of it is figuring out how the information is going to be understood, and I know you've talked about that, and I want to talk about it just a little bit more. Unfortunately, the FDA is not really great at working at getting information to be understood by patients or even by physicians. And having worked on FDA issues for many years, I've seen patient booklets that were approved by the FDA that are intended to explain to patients what the risks and benefits are of a particular medical device. And I've seen patient booklets that are 50 pages long, written really at a graduate school level, extremely technical, very complicated, and really not consumer friendly in any way, shape or form.

But, on the other hand, I think that FDA needs to get better at this. National Cancer Institute and many other institutes at NIH are much better at providing patient information and parts of FDA are getting very good at it, the Office for Women's Health, for example. So I think that FDA needs to do a much better job at explaining information and figuring out how to do that and figuring it out in a way that really will make a difference

so that people will understand it.

I believe that the standard for these kinds of tests should actually be higher than they are for tests that are interpreted by physicians, not because I think physicians necessarily do such a great job in explaining it, but at least they are better able to understand it. So I do think we could improve these kinds of tests for use with clinicians and other health professionals, but still I think the ones for patients need to be held to a higher standard because the risks are higher and the benefits are a little bit more questionable, and I say that as somebody who spends a lot of time working with patients, a very diverse group of patients, some of whom contact us by e-mail, some by letter, some by phone, some in person.

Some of these people can barely get through a sentence without grammatical errors and spelling very simple words incorrectly. Others are extremely knowledgeable and intelligent and have done an enormous amount of work trying to understand the medical information that they're trying to process.

But, regardless of how their spelling is or how their grammar is or their education, some people are not just very good at understanding risk information. They really don't understand it, and no matter how you try to explain it to them, it's very, very difficult, and other people are very good at it. So you're dealing with people who are coming to the table with a wide range of abilities and expertise.

So we talk to people who can barely read and people using these tests, some of them are going to be in that situation, barely able to read or barely able to read English or whatever language the results are going to be in. We talk to people who are barely able to understand risk information, and there are going to be people like that getting these results. And we also talk to people who are depressed or stressed out or in some cases mentally ill, and I'm not saying that everything that is done has to be done to the weakest among us, but there is a lot of people who are depressed in this country and who are concerned about genetic makeup and screening, and there are people who are spending very large parts of their lives caring for family members and loved ones with some of these diseases, and that's why they want to be tested for themselves.

And you can't assume that results aren't going to have a considerable impact on their mental health. So, you know, I can't agree with the idea that people won't be anxious. Some people won't be anxious. Some people will be extremely anxious. Some people will even be potentially very depressed and even suicidal if they think that they're going to end up like their loved one who is terribly debilitated by a genetic disease that they have.

So we can't protect everyone, and I'm not talking about this as a paternalistic point of view, but it is the job of the FDA to do its job, to weigh the risks and benefits and make sure that the benefits are going to

outweigh the risks if a product is used as directed.

So, in conclusion, I just want to say that, you know, this is a complicated issue. That's why you're here. I wish there was a simple answer. There isn't. But as you consider the standards that companies should be held to, who are looking into, who are doing these kinds of tests, who are selling these products -- it's fine that people want to make money selling their products. That's a very big part of why the FDA regulates these products and all other products. So that's fine, but we still need standards that protect patients, to do the very best that can be done to make sure that the product is as accurate as possible, that it actually has benefits that outweigh those risks, and that information is provided in a way -- and I don't think we can force people to go to a doctor to get the information from a physician or another clinician, but we can regulate products so that their test results are simpler. I think a pregnancy test is a pretty good example of that. It's pretty hard to misinterpret although I'm sure some people do. But to do the best we can to make the information understandable by the maximum number of people and to minimize the risk for the people most likely to use it. Thank you.

DR. WATERSON: Thank you. Our next speaker is Chantal Hemens-Davis.

MS. HEMENS-DAVIS: Thank you for providing me with the opportunity to share our thoughts with the Panel. My name is Chantal

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Hemens-Davis, and I'm responsible for quality and regulatory affairs at DNA Genotek. We're located in Ottawa, Ontario, Canada.

DNA Genotek is a leading provider of sample collections, stabilization and preparation products for research and testing applications. We have thousands of customers worldwide. Starting in 1994, we enabled our customers to conduct genome-wide association studies.

I would like to address the Panel with a slightly different scope of consideration than has been discussed over the past 2 days. While at times the discussion did touch on the DNA sample source used for direct-to-consumer testing, and for obvious reasons and necessary reasons, the vast majority of the focus has been on the validity of the tests and potential impact to consumers who receive results without practitioner involvement. What I would like to bring forward today, as we stated yesterday, is the need to include sample collection standardization within the oversight guidance.

In order to provide customer access to tests, many of the companies that currently offer direct-to-consumer testing rely on noninvasive sample collection to front end their service. While traditional testing and many LDTs rely on a blood sample for the test, for genetic-based testing, a noninvasive sample type, such as saliva or buccal, are also viable. Noninvasive collection essentially enables a whole new business model while also being an option for a convenient and patient-friendly point-of-care collection.

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Saliva-based samples enable anytime/anywhere sample collection, whether at home, in the clinic or in the field. It is safe for transport via the regular mail, which makes it ideal for direct-to-consumer-based or research-based applications. Surprising to many is the fact that saliva-based samples provide enough DNA to support complex arrays, and like buccal swabs, saliva-based samples contain not only buccal cells but up to 74 percent of the sample is composed of white blood cells.

I want to share with you an example of the impact saliva-based sample collection can have on health-based applications. The Anthony Nolan Trust is a UK-based charity whose objective is to find matches for leukemia patients who need a lifesaving transplant by establishing a bank of potential donors. While the Anthony Nolan Trust is not a direct-to-consumer company, there are some similarities between their model and that offered through DTC companies in that they largely rely on an online medium to recruit applicable candidates for the registry.

A question was raised yesterday in reference to Colleen McBride's presentation on the Multiplex Initiative about the potential impact that blood being the acquired sample type had on the overall results. What I'm sharing with you now is data that was provided to us by Anthony Nolan Trust after they changed their collection method from blood to saliva.

The Y axis indicates the number of samples collected while the X represents the calendar year. From 2006 through 2008, their sample

collection results follow the same trend. The red arrow highlights the time point when Anthony Nolan Trust switched from blood-based sample collection to saliva.

One can see the dramatic impact that noninvasive collection has on expediting sample collection for the registry as demonstrated by the thick blue line. The dotted line extrapolates an annualized view on the impact of noninvasive sample collection.

We believe that standards and thoughtful regulatory oversight should extend to the sample type that's being used for direct-to-consumer testing. As such, we have actively worked with the FDA and plan to submit our 510(k) in the coming weeks. Because we believe so firmly in the importance of ensuring the maximum performance of the sample type being used for genetic testing applications, we wanted to share with the Panel the elements that are important criteria for consideration in selecting non-blood-based samples.

Factors to consider in the selection and implementation of a sample acquisition strategy must support the overall quality and value of the test service that is offered. Sample collection methods should be able to provide data that supports, one, quality: Does the manufacturer of the device satisfy industry standards such as ISO and the FDA quality system requirements? Have the manufacturing processes been validated?

Active versus passive sample donation, as discussed at

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multiple times in yesterday's conversation: Is the patient/consumer required to do something active to provide a sample, thus minimizing the opportunity for a sample from other than customer is collected?

Has safety and effectiveness been proven for the device according to regulatory guidance? Has the collection method been widely adopted and demonstrated to be reliable for genetic applications? Can the sample withstand normal transport and storage condition fluctuations without having an impact on downstream performance? Interfering substances, is there a demonstration that neither endogenous or exogenous substances have an impact on the test results and performance?

In summary, I would request that the Panel include sample quality and integrity in consideration of the end-to-end quality for all genetic testing applications. Thank you.

DR. WATERSON: Thank you. Our next speaker will be Ed MacBean.

MR. MacBEAN: Good afternoon. My name is Ed MacBean. I'm the vice president of product development for Pathway Genomics Corporation. Pathway Genomics operates a CLIA-certified laboratory that began selling genetic tests directly to consumers in March of 2009, and then voluntarily suspended DTC testing while we worked with the FDA to address concerns about our services.

Yesterday, several Panel members voiced concerns that

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patients will not be able to fully understand the information provided in various reports, and I would counter that the responsible DTC companies have recognized these challenges and worked extremely hard to address those concerns through the design and content of our reports and to clearly communicate what genetic reports mean and do not mean.

Yesterday, we saw some of the ways that Navigenics and 23andMe present information graphically and breakdown complex topics into clear visual displays.

For our part, Pathway has opted not to report the statistical numbers of adjusted lifetime risks because we felt that those were difficult for customers to comprehend, and instead bin the results into quartiles based on appropriate levels of action or response. Most conditions will typically fall into what we call a learn more category, where patients are advised that their genetics are not indicative of a significant increase or decrease in risk, while a handful of conditions will typically fall into the categories of be proactive and take action, encouraging education and suggesting possible steps toward prevention.

Additionally, Pathway encouraged our customers to complete a lifestyle survey which was used to calculate a lifestyle risk bin and a family history used by our staff of clinical geneticists in reviewing the results and preparing communications to the consumer.

Ironically, as we moved away from a DTC model into a

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physician-centric model, collecting this data has become much more difficult as patients do not create online accounts through which they can provide and update that data.

Additionally, I want to point out that Pathway made a conscious decision not to test the most complicated conditions like Huntington's disease or other monogenic dominant conditions, exactly because we recognize the concerns raised by Nancy Wexler yesterday.

Finally, all the concerns about the patient experience in a DTC model seem to be operating under an assumption that patients have perfect understanding of their test results, the limitations, and their options when they are presented by their physician, and that these issues are being newly introduced as a result of DTC testing. I feel confident in stating that many patients leave their physicians confused and uncertain about the results.

Before getting into our proposals, it's important to establish a framework for our presentation. Pathway Genomics believes that people have a right to their own health information and that doing so can help consumers to improve their own health and wellness. At the same time, we acknowledge that genetic information is not free of risks and that the FDA has a responsibility to protect the public and ensure that information is accurate and delivered responsibly to patients and their caregivers.

I would like to reintroduce a slide presented last year by my colleague, Dave Becker, Pathway's chief scientific officer. As he pointed out,

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there are different categories of genetic reports, and as we move across the chart from left to right, the levels of possible consumer risks increase.

Certainly information like ancestry or traits is not considered to be high risk by most people, though as we get into information like dominant monogenic diseases or drug response that might alter treatment plans, the concern for possible risks increases.

I would like to add an overlay to this slide showing what we would consider to be a critical distinction. Information to the left of this line is typically and commonly given directly to consumers through a variety of channels, including risk calculators, websites, news and other media outlets, helping them in wellness and prevention; while the information to the right of line is commonly used by physicians, genetic counselors, or other clinical experts in the diagnosis and treatment of disease.

While trends may continue to push this line further and further to the right, this bifurcation of genetic information is an important distinction that should be considered in any regulatory framework.

Secondly, genetic testing consists of applying analytical models to static health information, being an individual's genotype, and as such, deserves consideration of a different type of regulatory review. In general, all the leading DTC companies supply an analytic process that applies a patient's genotype to research studies and, as such, they're able to expand their services by applying new research into the same analytical processes.

They can increase the value of their services by making more current research available to consumers and providers and by reporting on risks for a broadening panel of conditions and medications using the same static patient data.

So rather than reviewing individual tests, it would be more beneficial to analyze the algorithms and analytical models, looking at the ways that companies like Pathway select and calculate odds ratios, our criteria for selecting and qualifying markers for inclusion in the reports, and how that information is presented to users. Then as new data is published that fits into that established framework and the approved models, that information can be made available to consumers and healthcare providers in a system that is flexible enough to keep pace with the rapid rate of discovery of genetic information, allowing competitors to compete and innovate to make the best products and services available to consumers and providers, while still ensuring that the information is reported accurately and responsibly.

Finally, we would recommend establishing a mandatory registration database for all medical devices which would provide automated guidance on the proper regulatory path and requirements for a given product. Registering in this database would require companies to provide information such as our CAP and/or CLIA registration numbers, while also addressing specific questions from the regulations such as if our product is

intended for the diagnosis, cure, mitigation, treatment or prevention of disease, what type of information is being generated, how the device is being marketed, if and how clinical oversight is being provided and how the product is being distributed.

Obviously the questions listed here are just a small example of the questions that would need to be provided. But based on all the information about a company's products, support services, marketing and distribution plans, the FDA could provide unique identifiers for the product along with automated guidance on the appropriate regulatory path and specific directions on the rules, disclaimers and labeling needed to be used within that regulatory path. For example, if Pathway had been able to describe our relationship with Walgreen's in a system like this, we could have been informed that this product was not approved by the FDA for retail distribution versus the uncertain regulatory situation that we treaded into and are still discussing today.

As part of this automated system, we also recommend the FDA establish a clear categorization system to clearly communicate the recommended level of clinical oversight for any product. Our examples may not cover the full range of possible outcomes, but the system could clearly delineate if a product requires medical supervision, if it is recommended but not required to be supervised by different types of clinicians or if it is approved for use directly by consumers.

Vendors would be required to clearly provide the unique company and product identifiers on all products and communications. This information would be searchable on the FDA site and could easily be incorporated into smartphone applications that will allow consumers and providers to look up the registration information and guidance provided by the FDA. This categorization system would indicate the recommended or required level of clinical supervision, and the FDA could engage providers and consumers in identifying and reporting the bad apples that are inconsistent with the registration information.

The value of a registry goes much further, providing insight into the activities in the marketplace and identifying emerging issues that can then be used to contact vendors or industry leaders with areas of concern. A system like this could also be responsive to emerging technologies, incorporating new guidance into the system as studies are published on the actual risks of certain technologies and business models. There would need to be a process for appealing the guidance by industry and advocacy groups, but any changes to the guidance will be applied consistently across the marketplace for companies and products with similar profiles.

In conclusion, I would first like to reiterate Pathway's position that people have a right to their own health information, and that doing so, can improve the health of individuals while helping to lower the total cost of

healthcare.

Secondly, genetic information covers a range of current and emerging types of knowledge, much of which is already regularly presented to and processed independently by individuals in making personal healthcare decisions.

Third, genetic information presents possibilities for analyzing static personal data against dynamic research data in reproducible ways and, as such, deserves novel methods of evaluation that investigate the rules and methods of handling that information.

And, finally, we believe that a mandatory medical device registry could offer consistent and standardized guidance for the appropriate regulatory paths of innovative and novel technologies, while also collecting and sharing data that could make vendors, consumers and the FDA more informed while also being flexible and consistently incorporating novel technologies, business models and delivery methods into this process.

Thank you very much.

DR. WATERSON: Thank you. Our next speaker is Rose Romeo.

DR. ROMEO: I want to thank the Panel for the opportunity to be able to speak today. For the record, my name is Rose Romeo, and I'm the Senior Director of Regulatory Affairs and Quality Assurance at 23andMe. I also have to confess that I'm a recent addition to 23andMe. So there's a high likelihood that those layoffs that you heard about yesterday were likely

due to the ongoing proactive recruitment of individuals like myself with experience in both clinical laboratory medicine and diagnostic product development.

That said, my objective today is to continue upon the conversation initiated during yesterday's session by the general counsel of 23andMe and my colleague, Ashley Gould. The specific focus of this part of our collective presentation is to provide the views of 23andMe on items 2 and 3 of the Federal Register announcement for this meeting.

Being mindful of time, I want to move directly to slide 3, where we provide a risk assessment of the three risks put forth in the Federal Register, namely, the provision of incorrect data or misinformation, and information or data that is either miscommunicated and/or misunderstood.

Now, while many in this room may disagree, I would like to reiterate the fact that to date there is little evidence to show that these risks pose any undue concern or harm to consumers. However, any risk assessment worth its weight in gold is an iterative process. The mitigation should be defined up front and continually revisited to ensure effectiveness, and with that in mind, 23andMe provides a list of proposed mitigations for moving forward that we view as a robust set of controls to enable genetic testing to move into a well-defined regulatory framework, and this includes the subset of direct access testing.

You've heard many people talk about analytical performance. It goes without saying that this is an initial must have. We cannot have a discussion about clinical validity specific for genetic testing without analytical performance standards starting from the collection of the sample through the very last piece of code that spits out the report, be it on the web or directly to the customer.

We also need a regulatory framework, however, that will be able to incorporate the unique aspects associated with genetic testing. This includes those ongoing new genetic associations that are, you know, showing up on a daily basis. Someone in the past presentation says, do we need to wait for everything to be perfect? If that's the case, how do we keep innovation moving forward?

We also need to have a process in this regulatory framework and mitigation list to accommodate the new technologies. Right now we're dealing with the challenge of how do you set up a study design for a testing process that has a million SNPs. That's going to be a very tiny number in the very near future. So how do we collectively and collaboratively move forward in the definition on the most efficient types of study designs.

We've already touched basically on education within the regulatory framework. We view educational tools as a key instrument for mitigating risk. We have many in place now, but we also acknowledge that we can always do better, which is the tenant of any robust quality system

approach. Those educational tools in turn translate into the points on labeling that were discussed earlier today.

With regard to the customer service, I won't delve into the details that's already been mentioned; however, one of the exercises that we are in the midst of, as we speak, is implementing the quality system requirements over the preexisting processes within our existing CLIA quality system. From my past experiences, I can state that if done appropriately, it adds value in terms of reducing risk but it also adds value to the business model.

Last, but not least, is the availability of genetic counseling services and the appropriate prompts for physician interaction. This obviously needs to be a collaborative approach moving forward, but the discussion needs to happen now. So that way we can move forward and then improve upon our existing predefined mitigations.

The broad benefits from these mitigations will benefit not only consumers and healthcare professionals, but also direct access testing companies and regulatory agencies. I personally do not think it's a bad thing to be able to reexamine and revisit the FDA quality system processes as they relate to CLIA processes. There are definite add values in that aspect.

In turn, this will require all direct-to-consumer companies to perhaps engage in, what does a FDA quality system have to do with me? That can only aid in the ongoing collaboration between these companies and

the FDA.

Last, but certainly not least, is that if we move forward with these mitigations in an ongoing collaborative manner, we can only increase the confidence and understanding of genetic testing by all parties involved with the utilization of such data.

With that in mind, I'd like to move forward to touch again on a couple of mitigations mentioned by my colleague, Ashley Gould, yesterday. And that is that we already have in place videos provided in response to specific genotypes as well as training materials for the interpretation of personal data. We review these for improvements on a periodic basis and we see this avenue as one of the points where we can enter in a collaborative approach with consumers, healthcare providers and professional societies, not only to improve upon what we already do, but also to enter into spaces not yet investigated, such as CME and other related professional educational opportunities.

Finally, with regard to item 2 in the Federal Register, I'd like to touch upon the research communities. We have not only the research communities here that connect individuals with similar conditions and symptoms, but consolidating that input with the 75,000 individuals who have already elected to embrace direct access testing provides a unique asset and opportunity for us to contribute in the definition of this regulatory framework, so that we can address these points well taken over the last day

and a half, namely, what is the definition of clinical validity for genetic testing, and how can we take these points and further contribute into tools to enable more robust product development by all?

At this point, I'd like to switch to the slide addressing item 3 in the Federal Register announcement and looking at just what type of scientific evidence is appropriate for direct access genetic testing.

The fact that we're all here easily answers the point that the current IVD paradigm just isn't a perfect fit. I need to clarify by saying I am not saying that analytical performance standards should be relaxed, or am I saying the clinical validity is not important, rather that the existing paradigm right now is not enabled to address next gen sequencing nor is it able to enable easy discussions on just what to do with all the data. We also need to be able to have a paradigm that can address these scientific updates that are ongoing.

Taken all together and moving forward with the outputs that I list here, including the analytical standards, the consideration of inclusion of new technologies, the definition of a clinical validity point that is specific for genetic testing, and the definition of appropriate guidance documents and tools, can enable us all to move forward. At which point, I want to take and move to the final slide of my presentation, for proposals for moving forward.

Even with all that has been discussed to date, I would like to propose that this Panel move forward with recommendations to the FDA for

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the creation of a regulatory model that promotes innovation rather than inhibits it and is sufficiently flexible enough to evolve with research and technology within the space of genetic testing. One of the requirements of this regulatory model would be to establish clear requirements for both analytical and clinical validity and ensure that there is transparency that applies to all providers of genetic testing services.

Last, but not least, is that this regulatory model should include an expansion of educational efforts, not only capitalizing on more of what we do, but also how to be more creative in a collaborative manner in moving forward, be it through CME or other avenues yet to be defined.

Finally, I'd like to conclude by saying that I believe 23andMe has provided a list of mitigations today for consideration that we view as sufficiently robust for moving forward in a well-defined regulatory framework that will enable all genetic testing, including the subset of direct access testing, to move forward with success. Thank you.

DR. WATERSON: Thank you. Our next speaker is David Mongillo, if I got that right.

MR. MONGILLO: I'm David Mongillo, Vice President for Policy and Medical Affairs at the American Clinical Laboratory Association. ACLA members, we very much appreciate the opportunity to provide comment, and our members recognize that genetic testing is a cornerstone of personalized medicine bringing us better targeted and more patient-

centered care. This approach is translating into longer lives, better quality for patient with leukemia, multiple cancers, heart disease, HIV and many others.

Members of ACLA are proud to be at the forefront of delivering innovative genetic tests in partnership with healthcare providers and the patients they serve. ACLA clinical laboratory members perform genetic testing services but do not market those services to consumers or patients or customers. Testing is performed in clinical laboratories regulated by the Clinical Laboratory Improvement Amendments of 1988, or CLIA.

When genetic services are marketed and delivered directly to the consumer, without important input before and after testing from a qualified healthcare provider or genetic counselor, gaps in understanding can result in serious negative consequences. Consumers should rely upon the advice of a qualified health provider or a genetic counselor to identify which genetic tests are appropriate for the purpose for which testing is being sought and to understand the implication of the test results.

Some DTC entities are marketing testing for the propensity of developing disease condition, which often involves providing a statistical estimate of the risk of a medical condition or disease in the future. This type of testing may be informative but requires enhanced communication between the consumer and a qualified healthcare provider or genetic counselor so that meaningful action to reduce the chance of developing

disease can be taken and to avoid unintended adverse consequences. In particular, consumers might easily conclude that a medical condition or disease for which a future risk is predicted, even as a remote possibility, will absolutely occur in the future. Such risks may never come to fruition, even with above-average risk. Thus, consumers could be confused, frightened because they may have limited understanding of the meaning or real significance of the test results. These unintended consequences can be minimized when appropriate medical personnel are involved in the test ordering, reporting and consultation, as appropriate.

Clinical laboratories are currently regulated by both CLIA and state agencies. There are additional safeguards that ACLA requires of its member laboratories, including the requirement that its members gain accreditation by an independent CLIA organization such as the College of American Pathologists. Such independent accreditation provides important additional assurance that patients are receiving the highest quality testing and result information. Moreover, it supports compliance with state and federal laws governing the process of test ordering and result delivery.

DTC entities themselves are not all CLIA regulated and some appear to be making claims that may be misleading. ACLA supports state and federal investigations by the appropriate authorities to determine whether DTC entities are in full compliance with all applicable regulatory requirements and that the test claims can be substantiated and are not

misleading. The U.S. Federal Trade Commission has the authority to investigate any advertising claims and take action should it find they are false or misleading. DTC advertising should include all relevant information regarding capabilities, limitations of the tests, and contain a statement referring patients to qualified health providers or genetic counselors to obtain further information.

We thank you.

DR. WATERSON: Thank you. Our final speaker this afternoon is David Dunn.

MR. DUNN: Good afternoon. My name is David Dunn and I'm a regulatory affairs professional. I'm an independent consultant today, but I did spend 40 years as an IVD industry individual, and if you calculate that, that was before FDA actually regulated us. So since the time FDA has begun regulating the industry, I have been involved in lots of activities in that industry.

The last 18 years, I've been with companies or have advised companies that are in the genetics-based business. I just want to give you some brief background of what I've been involved with.

My first involvement was with the first home use product for blood glucose monitoring, and just as an aside, I stood in front of a Panel about this size in 1979 or 1980, and the same outcomes were there. The doctors were afraid to give us the authority and the responsibility to take

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care of our own health so they didn't want home blood glucose monitoring.

In addition, since I've been in the genetics business, I was responsible for the first tuberculosis test that was genetic based approved by the FDA. I was responsible for the first HIV and HCV assay approved by Siebert for testing the blood supply, and lastly I was with the company that published the human genomics information. I also have done CF. So I have a lot of experience working with companies, helping them convert their scientific discoveries and their information into viable medical products through the FDA process.

For the last 5 years, I've been advising small to medium-sized companies on how they can get their products through the regulatory process. Many of them don't have their own regulatory professionals and, as such, I hope that I've helped a lot of them move forward with these innovative and wonderful new products.

Last July, I was approached by a DTC company to help them navigate through the regulatory processes. That company was 23andMe, and they are reimbursing me for my travel here today and yesterday.

I had a lot of trepidations in saying yes to helping them, and the reason I did was many of my colleagues and I have discussed the DTCs and whether or not it's appropriate for them to be out there introducing products like cystic fibrosis without going through the same regulatory processes that we, as IVD members, have had to go through. And I was very

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happy to hear that FDA is going to regulate them and I'm hoping that we can work out a good process to help bring quality, that actually is already there in many instances, to the process and remain as direct-to-consumer.

So as I've done several hundred times before, in making my decision to work with 23andMe as a consultant, I decided to do a risk analysis. This is what I would do with any new product in any company that I represented. And the first thing I did is I sit down and said, okay, what can go wrong? Because we all, as regulatory professionals, have used risk analysis as one of the primary processes we use to begin the process of developing products and putting mitigations in place. I spent a lot of time on this. Normally in a company, there would be 15, 20, 30 individuals in a room batting these things around, but I just did it myself because this was my decision.

The first risk I was thinking about is what if the individual gets the wrong genetic information? And that's what we've been talking about quite a bit here, and that is the analytical performance of the assays, and I don't think there's any new information I can provide for you today, but the FDA has a very rigorous process. They do ensure that the claims that the information that the individual receives when they go through the regulatory process is as accurate as is the technology can provide today. So I kind of dismissed that because the company, 23andMe, has said to me, we want to go through this process; we want to be regulated by the FDA.

The second thing which I've heard a lot of discussion about is risk, risk of individuals, people, getting the wrong information and getting the information that could be harmful to them. So I gave that a lot of thought and I decided that there isn't, with a few exceptions, there isn't a lot of harm that anybody can do to themselves unless they seek advice from a medical professional, a physician, an educator, a nurse, whatever. So I kind of dismissed that as a serious risk to going direct-to-consumer, except, as I say, except with a few exceptions.

Those exceptions as I thought through them were mostly drug related and what the genetic information could do to a person that's taking drugs and the effects those genetics have on those drugs. So I would put that in a higher risk category and be very cognizant of that information.

On the other hand, as a person who one of these days may have to have warfarin therapy to extend my life any time period, I would want to know personally if I had those mutations that could create a problem with warfarin therapy and to, not necessarily run to my doctor and say, here, put this in my medical record, but to keep that for myself to know that if I my physician ever did say to me, you need to go on warfarin, I would be armed with that information to provide to them.

We've heard Huntington's disease several times here. 23andMe does not offer that as a screening test, and that's because of several issues, many of which have been discussed here, but it is not part of

their screen. And as far as I know, there's very limited companies that do that as a screen.

And I would like to talk about those things that could have medical harm. FDA has a lot of processes in place, and you've heard about many of them, labeling, compliance, guidances, genetic counseling. You've heard about requirements to access live genetic counselors. I believe that these are very important mitigation steps that need to be applied in the regulatory process to the information the consumer, the person that's buying this service.

Lastly, what about bad literature? I know that you, as scientists, are doing a lot of research, and I personally have experienced many articles that frankly were not good science, but they were still published. We believe -- I believe, in particular, that the risks involved with information being provided to the customer can be mitigated heavily through several things.

First of all, the curation process. 23andMe has a curation process that they go through, which is a rigorous review of the literature to determine whether or not they're going to put that on their report. This curation process really ferrets out a lot of the bad science and bad information and they don't put it there on their website or test for it until the curation process is completely done. I believe FDA can work with the industry and put together a document on curation process as a guidance

that everybody would use in order to bring new information to the direct-to-consumer testing.

There's also labeling requirements that we've heard about before.

So when I went through the process of looking at risk, which as I said, I've done many times before, I made the decision to go and help 23andMe bring their product through the regulatory process.

I also looked at the value. Ten years ago, a company I worked with at the time published the human genome, and I remember thinking at that time and many of our scientists said, "Amen, brother. We now are going to get personalized medicine." That was 10 years ago, and we still don't have personalized medicine. I heard a comment yesterday that it's not time for personalized medicine, but I maintain that until you start, it'll never be time. And DTC is the first that I'm aware of, ability to have a person understand what's in their genes and begin to discuss that with their physicians and develop a risk model for themselves, maybe prophylaxis, maybe change their diet, whatever the case may be. But it's just one element.

Sorry. I'm seeing the stop. My apologies. I will conclude at that. Thank you for your attention, and thank you to the FDA for giving me the opportunity to speak.

DR. WATERSON: Thank you. Thank you, everybody, for

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keeping it within the time limit. I appreciate that.

Did you want to address anyone, Alberto?

DR. GUTIERREZ: I just want to make a general comment. I just want to assure the Panel that the FDA actually tried very hard to provide a set of speakers that were balanced and that I would be surprised, despite the charges, the speakers themselves would have labeled themselves as anti-direct-to-consumer genetic testing. As a matter of fact, some of them have even been publicly written to be for it. So I just wanted to assure the Panel, you know, that we did consider, you know, and tried to give you a balanced set of speakers.

DR. WATERSON: Thank you. At this time, I'd like to ask, does anybody on the Panel have any questions for the speakers?

DR. RANSOHOFF: It's a comment and a question. Is that okay?

DR. WATERSON: Yes.

DR. RANSOHOFF: It's a question for Mary. I'm sorry, I forgot your last name. But I actually enjoyed your talk, and I wish that we had more time to talk about some of the points that you raised, and I've got a question at the end of just a brief comment.

First, I'm prepared to believe that doctors can be paternalistic and that doctors can make business for themselves individually and as professional societies. I think it's a very serious problem with the profession that we have to manage. I'm also prepared to believe that this Panel is

somewhat doctor-centric, and mentioned it to Panelists and to the FDA yesterday; don't know how important it is.

On the other side though, I think that there's something like a professional body of knowledge exists, and I'm really not sure, and this Panel sort of raises the issues, about where to draw the lines between knowledge that professionals build and manage and are custodians of, to use Louis Brandeis' term, the definition of what a profession is, and where normal human beings take over.

As an example, you mentioned, you know, we all get information in our lives and we live and manage it and so forth, and I want to tell you a very brief anecdote that illustrates the problem that I'm concerned about. It wasn't my life, but it was my mother's life. When she was a young girl, about 8 years old, somebody told her that she had a heart murmur, and for the next bunch of years she basically lived as an invalid. She would stay in her room. She wouldn't do athletics at school and so forth. And later she learned that it was a benign heart murmur and she really lost -- this affected her image of herself her whole life. You know, she's fine. She's a wonderful person and she's healthy and so forth, but she was really affected by that, and it's not genetic information but it is information and it caused mischief. And I don't know if it would have been picked up on a scale like we saw in *The New England Journal* a couple of weeks ago, but it's just -- and it's just one anecdote, but it's real life and it's

real information doing mischief.

There's other examples. I'm a doc and I see patients who take antibiotics and they conclude cause and effect when they could be doing themselves harm. I see people taking gluten-free or other diets that, in my view medically, aren't warranted; it might be a placebo effect that's making them better. But their lives are affected, and I try to figure out, do I just let them believe what makes them happy or do I try to intervene? How do I do that?

So just to get to the conclusion and a question for you. These people's lives are affected. It bothers me because of the paternalism in me, and I think the questions that I've put on the table are, are we really sure that there is no risk and no mischief here? I think it would have been nice, as you suggested, to have a thorough review of the evidence. To me, that's the critical question. And I know much recent evidence says there's no risk, but I would like to see that systematically looked for and systematically kept in mind. Because I know if you just label people as hypertensive, they miss more work even -- it was found out in a randomized control clinical trial. I'm worried about that sort of mischief, at the risk of being paternalistic, and I wonder if -- you know, what thoughts you may have. Are we really sure that there's no risk, and sort of, where do we draw the line? Is this really none of my business anymore as a professional and we let people believe what they want to believe? And given all that, do you have any general

recommendations for what you think the FDA ought to do? Is it no holds barred and we'll be a libertarian or where do you draw the lines?

Thank you for hearing me out.

MS. PENDERGAST: Thank you, and thank you for your candor. I think that -- I'm not sure I'm going to get it all right. I think that there is definitely a role for medical professionals. I think that they do have knowledge and they often have extra knowledge. The question is not whether or not there's a role for medical professionals; the question is whether or not they have a gatekeeping role. And I would submit that people should have access to information, truthful, not misleading information, analytically valid information, no lying, no cheating, no misleading, but that then it is up to the consumer to determine whether or not that person wants to avail themselves of the expert knowledge of the physician.

Just like with HIV or pregnancy, there's no requirement for the person to go get medical care, and I think that the same rule ought to apply here, where you cannot compel someone to go get medical information. Do I think you all have information to provide? Sure. But you're in the top 10 percent I'm sure. The latest survey showed that only 10 percent of physicians would know what to do if a patient brought to them a pharmacogenomic test result, and indeed the Center for Drugs part of the FDA worries deeply about the fact that they're labeling drugs with

pharmacogenetic information and that is not being picked up by the physician community.

So what would I do? I would insist on analytical validity. I would insist on clinical relevance of some sort. I wouldn't go so far as clinical utility. Almost none if medicine has to prove clinical utility before it is put out there. I would not expect the FDA to curate the content of every single SNP or, soon, every one of our 20 or 30 thousand genes in advance because that will stop this in its tracks. The FDA does not have enough resources. I would not demand that the FDA require a 510(k) or a PMA for every SNP. At one point they suggested that that's what they were going to demand. I did the math. The user fee alone would have \$34 billion for one client. So that's not doable. You know, as the Romans understood, the power to tax is the power to destroy.

DR. RANSOHOFF: Do we believe that there is no harm here and we don't have to worry about that, and if there was harm, is that important?

MS. PENDERGAST: I am willing to believe that there is harm. There are not good trials. The early questions were all -- and Colleen McBride is the expert on this. The early questionnaires of people all presumed there was harm, as in, how anxious did you feel or how upset were you, when the question should have been phrased, what, if any, anxiety did you have? So the early trials are all just sort of you should throw

them out.

The later trials show that people are themselves. If you're anxious before you get the test, you're going to be anxious afterwards. If you've got a more sunny personality, that will happen as well. Is there going to be anxiety? Sure. Does that mean we can't have information? No, I don't think that that's what it means. I think we all take risks. I think we all act in our lives on imperfect information. We choose to become firefighters, you know, we choose all sorts of things. You have to respect the rights of people to acknowledge that they're taking risks and then take it. Thank you.

DR. WATERSON: Anybody else have any questions? Kittie.

DR. WYNE: Kittie Wyne. I had a question for I believe it was the seventh speaker, Dr. Romeo. When you mentioned the training videos on the website, I just had a couple of questions about those. Is there any requirement for people to watch them before they can order their kit or before they can receive their results? Are they completely optional?

DR. ROMEO: My understanding -- and, Ashley, please pipe in if I'm wrong. My understanding is the videos as they exist in their current format is that if I were to spit in a cup and get my genotype back and I had a certain specific genotype, that that video would be customized for my genotype and be available to me the minute I brought my report up.

DR. WYNE: But it's not required before you're allowed to open your report?

DR. ROMEO: Not at this time, no.

DR. WYNE: Okay. Do you have any idea what percentage of people actually watch the videos or at least open them?

DR. ROMEO: I don't have that data right now.

DR. WYNE: I'm curious.

DR. ROMEO: But it's a good question. Thank you.

DR. WATERSON: Colleen.

DR. GALLAGHER: My question is for Mr. MacBean from Pathway. You had a slide where you showed how you would divide things into the different action steps.

MR. MacBEAN: Yes.

DR. GALLAGHER: Okay. And I'm wondering how -- you know, could you just describe a little bit about how you would delineate which results would go into which category?

MR. MacBEAN: Sure.

DR. GALLAGHER: Thank you.

MR. MacBEAN: It's a similar process to the ones described earlier by other vendors. We look at the odds ratios associated with the genetic markers for each condition and then the range of possible outcomes from the highest odds ratio, multiplicative odds ratio, down to the lowest, and break that information up into quartiles. So if your combination of genes would put you into the highest set of odds ratios, you would end up in

the highest of those four bins, whereas if you were not suggestive of -- you know, you had very low odds ratios, you would probably end up in the average bin.

DR. GALLAGHER: And would that mean, just as an example for my edification here, if you were doing a carrier test, for example -- I know there's some you don't do, but if you were doing a carrier test for something where the likelihood is that someone would be making a major decision, what would cause that particular type of carrier process possibly to take them up to the level of -- at the top you had immediate action. Would there be anything that would take you to that level?

MR. MacBEAN: First, let me clarify. Those bins were only for the complex health conditions. We're looking at things like types of cancer, risk of diabetes, heart disease and so on. Carrier status reporting is more of a binary yes or no, you are a carrier/not a carrier, for each individual condition that is tested for. So the carrier status test is not reported into those bins.

DR. WATERSON: Mary.

DR. MAHOWALD: Yes, this is a question for Mary Pendergast again. Obviously your basic rationale is to respect the autonomy of the consumer or customer --

MS. PENDERGAST: Customer.

DR. MAHOWALD: -- as I would like to say. And you said the

right to one's own knowledge. Does your argument go so far as to indicate that the customer also has a right not to know, not to be informed, for example, of some of the risks, not to be counseled in any way? Does it go that far?

MS. PENDERGAST: To the first point, I think that everybody should have the right not to know. I think the context in which we are talking are tests where somebody wants to know and searches out the test and finds out. So in that context, the person is seeking the information. The tests that I have seen on the thing, it goes: We have results for your blank. Do you really want to know? You should think about this for a minute before you decide because that might have implications for your life. If you really want to know, click here.

So it's a pause. It's an opportunity. But I do think that if people don't want to know. James Watson got his whole genome done but he didn't want to know about ApoE, right. That's his right. I mean, I believe that this is information about ourselves. It's like the 1970s Our Bodies Ourselves. If we want to know something, we get to know if; if we don't want to know it, fine.

Now, you've been asking -- and as long as I'm here, you've been asking about the rights of parents in getting their kids tested. That's a matter of state law. Each state decides what a parent can do vis-à-vis their child.

DR. MAHOWALD: Yes, I know, and laws are sometimes at odds with ethics, which is another point that could be made.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: Just to follow up on the risk categories. Are you saying -- I'm sorry, I don't recall the fellow. Are you saying those risk categories are completely uninformed by absolute risk solely based on odds ratios, that you have no idea of the absolute risk in those categories?

MR. MacBEAN: They are based on the odds ratios with the quartile for those odds ratios for that patient. It is not representative of the absolute risk.

DR. D'AGOSTINO: Just as a further comment. Sometimes you have a population where there's only like 4 or 5 percent that are really at high risk by absolute probabilities. You would be possibly declaring 25 percent at high risk if you break it up into quartiles?

MR. MacBEAN: No, I don't think we would be saying that. But you could have people for whom the genetic information -- 25 percent would be suggested that on genetics alone, there is an increase in their risk. But as I mentioned, we also provide a lifestyle risk which might suggest that on the genetics you are at a higher level risk, but based on your lifestyle, you're doing everything correctly and you are not at a significant risk. So looking at those factors independently and not trying to look at absolute overall risk.

DR. D'AGOSTINO: But it's all a make me feel good type of thing as opposed to really knowing what the absolute risks are.

MR. MacBEAN: I'm not sure I --

DR. D'AGOSTINO: Well, you know, I mean because the odds ratios can be very deceptive, especially where you get the odds, how you get the odds ratios. I mean it could come from a case-control study, for example, ultimately, and they could have very little bearing on the actual population risk in terms of what they're implying. You know, again, the ApoE was, when it first came out people -- when it was first bandied about, the odds ratios were monstrous, but it was because they were coming from databases that were case control and once we went to cohort studies, the odds ratios changed quite a bit.

MR. MacBEAN: Right. Well, I think our intent in the way we present our reports and communicate is to identify where the genetic information might adjust their awareness and concern of things they want to be concerned about, but not trying to indicate what their absolute risk would be.

DR. WATERSON: Majid.

DR. MORIDANI: I have two, three comments, no questions. One is that based on the observations I made, half of the Panel members are nonmedical doctors. They are Ph.D.'s. So that's one observation that I want to share with the speakers.

Second, personally I am in favor of DTC in terms of empowering consumers but I would like clinical validity, clinical and analytical validity, and also results to be highly regulated and to be sent back to the physicians. So I'm in favor of empowering consumers, and I think many peoples over here, they share the same thing. So it's not like, you know, 40 years back. So almost -- a lot of people feel that way.

And the third thing, the third comment that I have, many examples that I saw today, the -- that provided to us, all of them are clinical chemistry, like glucose, hemoglobin A1c, pregnancy, alpha-fetoproteins. You know, for pregnancy test, people who go for a pregnancy test, they are either planning a family or they want to prevent a pregnancy, or they have it or they don't have it.

So these comments just, I felt that it's more appropriate to make it at this time.

DR. WATERSON: Did you have a comment, Margaret?

DR. DAVIS: Margaret Davis, Consumer Rep. This is for the gentleman from American Clinical Lab Association. Was the first name David? You made a statement when you made your presentation that DTC entities are not CLIA-regulated. Is that substantiated or is it just a blanket statement? And if it is substantiated, what are the implications for the consumer?

MR. MONGILLO: The distinction I was trying to make was

between a clinical laboratory that's performing the analytic and, we believe, clinical validity service versus companies who are then taking the results of the information from that clinical laboratory service and marketing it directly to consumers. So the entity that I'm discussing in that regard is not a clinical laboratory, therefore not under the auspices of CLIA. I don't know if that helps, but --

DR. DAVIS: It does. Thank you.

UNIDENTIFIED SPEAKER: What was your name, sir?

MR. MONGILLO: Mongillo, David Mongillo.

DR. WATERSON: Gregory.

DR. TSONGALIS: So I really don't think we can take what's being perceived as the Wild Wild West and turn it into Mayberry, right. I think what we've seen from the speakers, and I think everybody did a great job, was if we could pick and choose certain aspects of each of the programs you all represented and put those together, I don't think many people around the Panel would have issues with direct-to-consumer testing. But I think we have to figure out some type of common ground between clinicians and labs and companies where we can bring all this together because there's really a lot more riding on this than just direct-to-consumer testing and a few companies.

DR. WATERSON: Ira.

DR. LUBIN: I have a question for Mary Pendergast. So your

position was extremely well presented. Thank you.

One issue I'd like to get some additional feedback from you is in terms of empowering the consumer with information, what is your view on who is responsible for ensuring the accuracy or usefulness of the clinical information provided from the company providing that information to the consumer?

MS. PENDERGAST: Well, as with all FDA-regulated entities, the ultimate responsibility is that of the company. So, for example, for accuracy, it is the company's obligation to be accurate, but the FDA will oversee that accuracy, at least the analytical validity of the testing. So that's point number one.

With respect to point number two concerning the usefulness of it, that is, I think, something that is to be fruitfully discussed. As you heard, some companies have a process where they require two published journals replication and, you know, subject sizes of X or more. Some of them have a robust way of analyzing connectedness to clinical validity. Other companies don't.

I mean to your point about the Wild West, I mean if you want to know what's going on out there, send FDA investigators. Many of these companies are simply dry labs and if you investigated, you'd find out that there's no equipment whatsoever. If you required analytical validity and sent around panels of analytes to be tested for proficiency sake, you'd wipe

out the next set, and then you'd probably have no Wild West.

DR. LUBIN: So the focus of the question is on the clinical validity piece. Making the assumption for a second that there are components of DTC that can really empower and be helpful for the population in general, the question becomes what entity, and here we have potentially the FDA, perhaps should have the authority to review that information to ensure or try to ensure its accuracy and consistency? Because not being able to do that could potentially compromise the advance of this area.

MS. PENDERGAST: That's a point. I mean, should the FDA pre-review every clinical validity thing? If you've got 600,000 SNPs, and you're reporting out as many as are reported out by all the laboratories on genetest.com, how long will it take for the FDA to pre-review everything everybody is saying? Is that going to work? Is there some other way that if you, (1) the test has been adopted by a professional society, (2) by NIH, (3) by CDC, (4) it's on the label of a drug, (5) something else, then you could say it? There's other models, other than having the FDA, company by company, SNP by SNP, test by test, not let anyone know anything until they pre-reviewed it. I think knowing the FDA's resources, it simply does not have the capacity to do that in advance. Thank you.

DR. WATERSON: Any other questions of the speakers?

Okay. So we're at the time right now where we can end the

public session.

Would people want to take a break now or do you want to take a break in a little bit?

We will take a 10-minute break now.

(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 are 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.

Dr. Mansfield, do you want to proceed with Question 3?

DR. MANSFIELD: Thank you, Dr. Waterson. I'd like to start with the clarification that FDA has at no time stated that it wished to regulate each SNP in the human genome. So you can be reassured of that.

Question number 3: FDA requires valid scientific evidence (typically with both analytical and clinical validation) in order to determine that medical devices, including home use and over-the-counter tests, are safe and effective. Results of clinical direct-to-consumer tests may be used in many ways, including for patient management, for health improvement, or for personal interest. Do these differences suggest different evidence requirements for supporting direct-to-consumer genetic test claims?

Part (a) of the question: Should analytical and clinical

performance characteristics for clinical direct-to-consumer genetic tests be different than those for genetic tests offered solely through physicians?

- Given the possibility of fewer risk mitigation options in direct-to-consumer testing than when the testing is offered through a physician, should direct-to-consumer tests in general have more stringent performance characteristics, for example, greater test accuracy?

- What are the appropriate evidence levels to support specific direct-to-consumer test performance characteristics?

DR. WATERSON: I saw your hand first, Joann.

DR. BOUGHMAN: Joann Boughman. Could I ask for one clarification? Here in the written question it uses the term physician in each one of these places. Is it inappropriate for us to at least in our minds change that to qualified health professional or do you mean physician?

DR. MANSFIELD: We mean qualified health professionals.

DR. BOUGHMAN: Thank you.

DR. WATERSON: Okay. George.

DR. NETTO: George Netto. So I do believe they should be held to the same standards as physician-ordered testing, definitely not lower standards, but the same standards. I think the main concern for myself and, I believe, for several of the Panel members is the interpretation issue. But as far as analytical standards and clinical utility and -- as opposed to what's

been implied in previous comments, physicians practicing in the United States do their best to prove clinical utility for every single action they do. So that statement is blatantly wrong because there is something called evidence-based medicine that people are in their statement ignoring.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: I'm not sure exactly what the question is driving at, that somehow or other the consumer isn't as smart, so the test should be better; or is somehow or other because it's going to the consumer, that you won't worry about it. But I think that some of the general rules that we heard about today, what the FDA requires and the input we've been given, that there can be a uniform standard that goes across these tests, as opposed to one test has better accuracy than another. I don't follow that.

DR. GREGG: This is Jeff Gregg. I totally agree with that. I think that these tests should have the same stringent requirements as the tests going to the clinical labs.

DR. WATERSON: I think the Panel members that have commented are sort of in agreement. They should meet the same standards that we expect for tests that are offered through physicians. I don't know about the higher standard. I understood the comments on the glucose testing where somebody -- it has to be more foolproof and easier to do, but I think these are tests that are generally going to be sent off to a laboratory,

and I think the laboratory should be held to the same standard.

DR. MANSFIELD: You could consider that a higher standard would be necessary and, for example, Marina just informed me that HIV testing actually has a higher performance requirement when offered over the counter than when by prescription. Is that correct?

DR. KONDRATOVICH: The CLIA waiver is different.

DR. MANSFIELD: Oh, for CLIA waiver, yes. So there are instances of HIV testing in which the performance standard must be considerably higher.

DR. WATERSON: Gosh, I'd like to know my HIV test was the same whether I did it myself or --

DR. MANSFIELD: When the consumer does it, the performance standard is quite tight because there are fewer risk mitigations.

DR. WATERSON: Okay. I think we're ready -- Ralph.

DR. D'AGOSTINO: What do you mean by -- I guess I'm not catching the discussion of what you mean. What does it mean by tighter? I mean, the test is performed, a statement is made from the test. What's tighter about it?

DR. GUTIERREZ: So let me see if I can get to crux of the question. We actually don't always require the same things of direct-to-consumer to physician order. One case in which we may go the other way is with glucose meters. We may -- we believe that glucose meters when used

in the hospital, are being used for directing therapy in a way different than users would do at home so we may actually require them to have tighter specifications.

We may also go the other way. If we think that the risks are such that in a laboratory there are controls that would not be had either at a point of care or in direct-to-consumer, we may actually believe that to control the risks in a what is less control realm, that you may actually have to have a better test, if you'd like, or more control. So the idea of asking you here was whether if you see any -- are there any reasons to believe that we would have to hold the direct-to-consumer genetic test to a higher standard of performance than when it is ordered by a physician? And the answer may be no, you know, maybe that's --

DR. WATERSON: Greg.

DR. TSONGALIS: So I'd like to think that the answer would be no, and I don't really think that would be necessary, but I think where you're going to run into problems is that we don't have really good established performance guidelines for some of the new technologies even in the hospital-based clinical labs. And so I think if the playing field is level and everybody has the same set of standards to practice by, then good laboratory practices I think will prevail on that issue.

DR. WATERSON: Great. Okay.

DR. HERSCH: I think the only thing I can think of that might be

an additional consideration is the identity of the sample, and just considerations of how to -- whereas, you know, if a sample is drawn, you know, in a phlebotomy lab, there's a pretty good degree of -- it's not certain, but fairly reasonable certainty that you know that sample came from the individual that it came from, and that's something that has a potential to get lost with DTC. And so considering how to safeguard that, I'm not quite sure what the answer is, but that's one place where things can be a little bit different. Again, that's more the chain of movement of the sample.

DR. WATERSON: Okay. Let's move on to the second part. I'm sorry. Did I miss a comment over here?

DR. LIPKIN: I'll wait.

DR. WATERSON: Sorry.

DR. MANSFIELD: What may be the advantages and disadvantages of providing a number of genetic tests bundled together (for example, certain categories listed in Question 1(a)), versus ordered separately for separate indications? And when we say bundled together, we mean tests that may have different intended uses and indications all ordered and returned for the same person.

DR. WATERSON: Mary.

DR. MAHOWALD: Well, an obvious advantage would be the cost, I assume.

DR. NETTO: Another advantage would be marketability, but I

can see some disadvantages.

DR. WATERSON: Do you want to state the disadvantages?

DR. NETTO: The disadvantages is if you want to build in, in the label the interpretation guidelines and all the details of the odds ratio, and having so many different tests in the same -- it's going to be a monstrous, pages and pages of things according to every test, different prevalence, different risks, different -- I think that's a big disadvantage that's going to make it prohibitive if the rules are going to be set in the way that we believe will be safe enough for the patient.

DR. WATERSON: Now, were these guidelines -- would this be satisfied, just all this information is on the Internet so you can review that for each individual test or do people have to get the whole 50 or 60 pages of insert?

DR. GALLAGHER: I think for me -- you know, we've talked a lot about how people get information, and I think one of the possible advantages, if done in a good way, would be if someone, and I'll make this up, what if someone said, okay, I want to be tested for something related to cardiovascular and I want to be tested for diabetes, things that we commonly see as diseases that cluster in an individual, which if somehow that comes together and can be pooled together in some kind of report that makes sense to them, then that may, in fact, be an advantage to the person who is receiving that information.

DR. WATERSON: It seems like to me that part of the intended use is to provide a profile, too. So you'd probably want multiple tests.

DR. WYNE: Kittie Wyne. I think that's exactly what the issue to me is with this question is, are you doing a specific carrier assessment, a specific gene assessment, or are you doing a risk assessment? And if you're doing a disease risk assessment, you're going to want multiple genes in your panel or whatever test you order. And how would you decide which ones to use? You know, that's kind of what the companies are putting together a panel and calculating a risk from the multiple different variants. That's the idea of the risk, I think.

DR. MANSFIELD: Let me refocus the question. In fact, we're talking about different intended uses without regard to the number of markers that are measured in order to make that claim. If you need to measure five markers in order to determine risk, then that's fine. We're asking whether tests with different intended uses, for example, different kinds of carrier screening or different risk tests, should be bundled together or offered separately.

DR. WYNE: So you're saying should they be allowed to just have the whole gene chip or should people be allowed to pick panels? Is that what you're asking basically, or both?

DR. MANSFIELD: I'm sorry. I couldn't hear you.

DR. WYNE: So I think the question is not, do you order which

one of the 100,000 tests? The question is, should people only get everything that's on the chip or should they pick the panels that they want or only be given certain panels? I think that's more of the question then.

DR. MANSFIELD: Let me refocus again. For carrier testing or for diagnostic testing, which in general admittedly is not offered by direct-to-consumer companies, there may be a number of different indications for use. For example, cystic fibrosis, Tay-Sachs disease, Huntington's disease, should those all be offered together at one time to a patient or should they be offered separately?

DR. WATERSON: Tiffany.

MS. HOUSE: I mean, I think it should be whatever the particular tests a consumer wants. I mean, if they want to be tested for everything, fine. If they want one, fine. I don't think it should be dictated one way or the other.

DR. WATERSON: Yes, Mary.

DR. MAHOWALD: What about unasked for information that is relevant to the person's health?

DR. WATERSON: I would think if you ordered the test, you'd better be sort of aware of what's on the test.

DR. MAHOWALD: Well, you know, people have, for example, brought up paternity as an aspect. So I mean, these occasions do happen when information is discovered that the patient didn't ask for that may be

relevant, and I just wonder how the companies would deal with that.

DR. WATERSON: Bob.

DR. SHAMBUREK: Bob Shamburek. I think we heard some of the public comments that with personalized medicine, they want to have that choice. So they may want to know about certain risk factors for heart disease but then again, it sounds like they want the choice not to know about cystic fibrosis. But I think this is going to be a big issue that I know people with protocols and IRBs and IRB has to deal with is the area of whole exome and whole genomic, you're going to get that information.

Now, there may be several actionable ones which could affect a person's life, and can you withhold that information because in order to get the cardiovascular and the hypertension and the diabetes, you might find something out about a well-described, well-known cancer or they have Huntington's -- we keep bring back. But I think the big issue is if you can pick and choose like a chemistry, I would want my chloride, but I don't want my sodium, but with whole exome and whole genomic, I think that's an issue of do you not disclose that information? And I'm not sure that's possible because we're hearing, and I would agree as a consumer, if I were one, I'd want all my data and I might want it reanalyzed, but the information is going to be there.

DR. D'AGOSTINO: Just so I am again understanding this correctly. I mean if the consumer is picking what he or she wants, then do it,

but are we worried about that the consumer may only have available a bundle and he or she gets what they want but they may get other things? Is that basically that the bundle may be bigger than what the consumer wants?

DR. MANSFIELD: That's one of the questions. Another is the question perhaps of prevalence in the population that you belong to. Some tests may be appropriate for your population. Other tests may have the possibility of giving you false information due to the rarity of an allele, perhaps, in your population. There are a number of different reasons for bundling or unbundling.

DR. WATERSON: Steven.

DR. LIPKIN: I was just thinking about also that the field is rapidly moving towards, you know, exomes and whole genomes. So, first of all, I mean the history of genetics is giving the patients, you know, the right to know what they want to or not to. So in terms of bundling, and I think this is sort of currently, at least some academic circles, the thinking of how we might approach exome sequencing, for example, and genome sequencing is going to be even worse or more of an issue. You know, I think that most medical services will not be prepared to actually deal with the full monty, so to speak, the full exomes, and the thinking is that, well, these are bundled into more disease categories, for example, hereditary colon cancer, autism, et cetera.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. I appreciate the fact that we are trying to think ahead with whole exome and whole genome, but with regard to the panels for the approvals now or next week or next month, I would just like to reiterate that whatever the company is proposing to test, that in the results and interpretation that they carefully and comprehensively include the data or the information so that the consumer or the interpreter has as much information as possible. And it's both a benefit and a risk and, yes, I don't know whether you've seen some of the reports, but they can be 150 pages long.

DR. WATERSON: Rochelle.

DR. HIRSCHHORN: Yes, Rochelle Hirschhorn. I would just like to remind you all that each of us carries at least six to eight mutations that are different from the disease-causing mutation that you're looking for, and it just reaffirms the necessity for having someone look at this and be able to interpret that. It would depend on which they would find and it would depend upon the particular setup that the company is using, but I think that we have to keep that in mind.

I think we also have to keep in mind that we don't know what over 50 percent of our genes are doing, and we don't know what most of our genomic DNA is doing. But I agree with you that we're going to have to wait and see and we should just move on to what we can do. Thank you.

DR. WATERSON: Ralph.

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DR. D'AGOSTINO: Thank you. When the approval is being made, is the approval done on the bundle or is it done on the individual tests? My question, where I'm heading, if the approval is done on the individual tests, then why can't the company bundle them if they choose to do so?

DR. GUTIERREZ: The company actually can sell them any way, even if their -- especially if their 510(k), after we approve them. We actually don't have a lot of -- exactly how they do it. We have a little bit in direct-to-consumer because we will be looking at, you know, the risks and stuff. The idea here is whether there are any risks that are brought on by the fact that a lot of tests are being given together versus being given separately.

DR. D'AGOSTINO: The potential for false positives may increase in something like that, that you're concerned about, information overload.

DR. WATERSON: Ira.

DR. LUBIN: So consider two types of tests. One would be, say, a cardiac panel that targets specific genes, perhaps specific variations, wherein the product labeling, perhaps in a complex matter, but you can likely account for most, if not all, of the potential outcomes from testing in that panel, and tests can also be ordered separately and there are laboratories offering these. So that's sort of one category where the labeling can explain a lot.

The second category is if you're doing broader sequence analysis, whether it be larger gene panels, exome analysis or whole genome analysis, in which there is the likely possibility that there will be findings that are not so easily interpreted and therefore it makes it more difficult in the package labeling to explain what may or may not be found.

Furthermore, in terms of sequence analysis and moving back to single gene analysis, several laboratories offering sequence analysis, really -- when they have a finding, they really want to serve their clients and try to communicate the likely meaning of that finding, and there are various methods to determine whether a sequence variation may affect the protein that that particular sequence codes for, and mention whether there's a likely or unlikely possibility that it's a sequence of clinical significance or not. And this is still an area that's in flux in terms of how it's approached by different laboratories. So that sort of bears that there's a category of tests in which you can define most, if not all, the possible outcomes, and then there's this other category that the new technologies are presenting where it becomes far more problematic in the package labeling, or otherwise, to consider the possible results.

DR. LEE: Just for clarification, I don't see any significant advantage to encourage or enforce unbundling of tests. I think I would leave that to the various companies to decide.

DR. WATERSON: Any other comments? Okay.

DR. MANSFIELD: Thank you. Moving on to now slightly more technical issues.

There is a need to develop efficient approaches for analytical validation of highly multiplexed genetic tests. One suggested approach (for example, for cytogenetic arrays that query the entire genome) is to select and validate an appropriate subset of genetic markers with an inference that the platform as a whole is analytically valid, assuming that you can validate those markers. Another approach is to explicitly validate each marker that is used in generating a test result. I'm going to take these questions separately.

- Please discuss the advantages and disadvantages of these (or any other suitable) approaches to analytical validation of highly multiplexed direct-to-consumer tests.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: This sort of takes us back to some of the other questions where I think it's very hard to say this is what should be done. There are lots of approaches that can be done in terms of having a panel of genes or SNPs and picking the ones with the lowest p level, the highest logged p, and then start doing subset analysis with them, basically; see if a random subset gives as much information as the full set, and then what I always find very important, I think the genetics type work that we're doing with Framingham, is to get another database that will reproduce what

you have. And there's a lot of that going on, and to try to sort of hone in on a particular method, I think we're not necessarily there, but the important thing is to keep control of your error rates as you're going along and have the ability, in whatever method you're doing, to actually control these error rates. And the two methods you give, if you -- the subset is a lot easier to do and manageable if you have a lot of genes to look at, and you start doing one at a time, you're just basically going to see all kinds of weird results coming up because of random fluctuations. It makes it very compelling to look at a validation data set. It also in some sense makes it, you'll never get anything going if you have too many to look at. So you have these broad screening methods. Then you can cull down to a set and then you start doing these internal validations and external validation methods.

DR. TSONGALIS: I think what the question was referring to, and maybe I misinterpreted it, is that you're referring more to technical validity, that is, if you have a chip that measures 500,000 SNPs, do you need to measure all 500,000 or you do 10,000 and rotate every month or something like that?

DR. MANSFIELD: That's correct. We are interested in determining in the technical -- or analytical or measurement validation, the highly multiplex technology. There are a number of approaches, too, that seem most likely to us would be an approach in which one simply chooses any subset of genetic markers and infers validation across the entire

platform, or whether one needs to validate at each point that will be of analytical and clinical interest.

DR. D'AGOSTINO: What I was saying sort of shifts then, not so much of the p values but to the -- it's still the same basic notion but now you're looking for the analytic validation as opposed to the p values, but you still have that sort of different sets of methods.

DR. WATERSON: Gregory.

DR. TSONGALIS: So I think this is going to be not impossible to do but really not an easy thing for labs to do, whether it's a company lab or any other lab, just because of the numbers of potential variants or SNPs that you'll be looking for.

The other thing to keep in mind, one of the exciting things about this is that it has the potential to generate a lot of data, a lot of data that could potentially be used for new associations with old SNPs. And depending on the technology, we have the capability -- or the ability to potentially even identify a lot of other variants that are not associated with anything right now. And so I don't think we want to limit this by the types of validation the lab's going to have to do.

DR. LEE: Being the only cytogeneticist on the Panel, I think I have to make a few comments here.

So the cytogeneticists currently are using a lot of array-based technologies for diagnostics. These involve a million markers or more on a

single array, and in most cases, they're really being used as screening tools. And so the question here is, do we advocate for testing for each of these probes that are on the array individually? And I think the answer, in my opinion, is, no, we can't do that. That's not efficient.

What we can do is something that's currently being done in the clinical cytogenetic diagnostic arena right now, and I believe it's Lisa Coleman, from the CDC, is organizing a group of cytogeneticists that are working together to develop a reference panel of DNAs that are being used to do testing on a two-tiered system. So one would be essentially clinical validation, identify those cell lines that have the most commonly identified genomic syndromes that we see in clinic and make sure that the various array panels can identify those accurately, and the second is to use some minimal number of cell lines that have large genomic aberrations that will sort of profile whether or not you can get a one-copy gain or loss across these arrays.

None of the labs that I'm aware of that are running these tests will rely on one or two probes in a row to make a one-copy gain or loss call. So in many ways, this allows us to infer the performance of the overall platform in a much more effective manner. So that would be what I would be advocating.

DR. WATERSON: George.

DR. NETTO: This is what I would envision, too, is that first

method, to select a representative of the panels because it would be impossible to do the entire thing. But I know down the road we have another question related to that. So I'll comment on that.

DR. WATERSON: Anybody else have any comments?

DR. MANSFIELD: Thank you. The next part of that question:

- If the first suggested approach, that is, selecting a representative subset of genetic markers to infer analytical validation of an entire platform, is used for direct-to-consumer test reporting on a number of different disorders, what strategy should be used to select the representative subset of markers?

DR. WATERSON: George.

DR. NETTO: So I think you need to read the two choices, right, because you list there, two choices.

- Should the subset be enriched with markers that pose an analytical challenge? And also

- Should it be a subset of markers from each of the relevant disorders?

In my opinion, it should include both. So it should cover all the relevant disorders, and for each disorder, the ones -- especially put some emphasis on the technically challenging one.

DR. MANSFIELD: Yes, thank you. I failed to complete the

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question. So let me read the choices that we provided.

- Should the subset be enriched with markers that pose an analytical challenge, that is, may be difficult to measure?
- Should the subset of markers include markers from each of the relevant disorders?

DR. WATERSON: Other comments? If there are none, I think most of us would probably agree that both of those --

DR. HERSCH: Just one --

DR. WATERSON: Steven.

DR. HERSCH: Yeah, one caveat. I mean, being representative of each of the relevant disorders may not be necessary or -- I mean, you know, how do you limit that? Again, that could turn into great numbers, then someone's going to have to do some selecting. It's probably possible to come to some reasonable size of things without requiring broad distribution. Of course, it will depend upon what the sponsor's test is actually going to test and what's going to be included. And so you want it to be both representative of what the test is testing as well as putting the platform to the test. So there would need to be some flexibility.

DR. WATERSON: Ira.

DR. LUBIN: A third criteria you might want to consider is the prevalence of the variants that you're looking at in there because you want

to ensure that the platform is able to pick up the most common variants likely to be detected in the population.

DR. NETTO: George Netto again. So I think another way around that would be rotating so at least you end up not leaving one of the disorders that you're testing for ever, you know, being validated. So you can consider that, but you should try as much as you can.

DR. WATERSON: Okay. Any other comments?

Okay. We'll move on to the next one.

DR. MANSFIELD: Are there any other suggestions for approaches to analytical validation that we haven't listed here? Okay.

- Would the adoption of the first suggested approach, that is, the subset validation, make it advisable to perform confirmatory testing of the results of highly multiplexed direct-to-consumer genetic tests?

And if I may clarify on this, that would be because you had not necessarily analytically validated all of the features that would be reported. You would have validated on a random or otherwise chosen subset.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: When I was responding before, I was looking at just validate as opposed to analytical validation. But it's easy to shift the things I was saying, that I think the validation component and the -- you know, we already addressed the subset there. But I think the question

here is that the validation would give you that aspect on another set -- a confirmatory test would give you that assurance that what you have done before, in fact, has a meaning to it, and I think it's a pretty important aspect in terms of the development of this analytic validation.

DR. WATERSON: Charles.

DR. LEE: So I just want to share with you two possibilities here. So with clinical cytogenetic testing, when we're talking about array-based testing, often a lot of labs don't make calls unless there's 25 consecutive probes in a row that show a one-copy gain or one-copy loss. These probes are randomly distributed throughout the genome. So the chances that all of those probes are going up or down is very unlikely due to chance alone. So for those kind of test results, there are a lot of labs that actually are not -- they are very confident, and I agree with them, that they're very confident that that is a true gain or a true loss.

When you talk about whole genome sequencing, for example, with whole genome sequencing and with current accuracies, most of the companies are quoting about 99.999 percent accuracy, and in those kind of situations, even with that level of accuracy, you are getting probably about 100,000 errors for given genomes. So I would actually say that it may be something that may warrant having confirmatory testing. So I think it depends on what platform or what testing that's involved.

DR. WATERSON: Joann.

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DR. BOUGHMAN: Joann Boughman. I would just remind us that the FDA for many years has worked against a gold standard for a predicate device, and I think what I'm hearing is that one of the mechanisms to get to or define the gold standard would be the industry standard or the high level lab standard agreed upon by a group of professionals. Then if that has not been established, I think we may be in the realm of the good news is somebody's on the cutting edge; the bad news is that the cutting edge sometimes bleeds, and the first ones there may have to do much more work in establishing a predicate device against whatever they determine in the literature at their best summary is the gold summary.

DR. WATERSON: Any other comments? Okay.

DR. MANSFIELD: Thank you. Now we'll turn back towards more clinically oriented questions.

For direct-to-consumer genetic tests, should a contribution of the genetic test result beyond the current risk factors (for example, family history) be required to be demonstrated?

DR. WATERSON: Ralph.

DR. D'AGOSTINO: I have to start on this one. I mean, I think that the presentation to the FDA and the database should take into account the information that's known about the phenotypic data, such as family history, such as in diabetes or a glucose tolerance test, and what have you. You know, I don't get to the point where I can see a warning saying this test

may give you no more information than blood pressure would or something like that. I'm not pushing for that, but I think that these tests should incorporate the signs of the day.

Now, asking them to develop a mathematical model that adds this variable and do all the stuff in terms of do you reclassify subjects in the correct way and so forth, that might be pushing it and overdoing it, but to have them cognizant of what's in there and does this really add beyond some basic risk factors, I think that that should be part of the goal and should be part of what is expected of them. You can't just look at this gene has a rate of events later on without saying, is it mitigated by environmental factors?

DR. WATERSON: George.

DR. NETTO: I fully agree with that and the reason behind it, too, can be because the environmental and phenotypical may actually trump the genetic in certain circumstances. So as part of full understanding, and truthful in reporting an interpretation, I think it's very crucial that this is going to add or, really, if you have other factors, this is probably not as important.

DR. WATERSON: Okay.

DR. MANSFIELD: Thank you. Direct-to-consumer genetic testing companies may validate their tests using results and information from current customers or clients or consumers, or however you would like

to put it. Important characteristics of this population may differ from the characteristics of the general population to whom the test is offered. What considerations, if any, are necessary concerning these differences?

DR. WATERSON: Ralph.

DR. D'AGOSTINO: Is this question different than what's the target population? I mean, because if it's -- you know, if we go back to, does it work on the target population, and somehow or other that makes it approvable, or whatever vocabulary we want to use, if we can't talk about approvability, but that makes it, you know, sensible.

The question becomes a generalization, to whom can you generalize these results? And I think that gets us into different populations and validation on other databases and so forth, which we had mentioned before. I'm not sure I, you know, would have an answer to this because if you, again, look at the absolute probabilities as the way to present this and divide the individuals according to low, medium, high risk, that might work in transporting, but unless you have the validation from an independent population and the odds -- excuse me, the absolute risk and the relative risk, you don't know that answer, and so I don't really -- I mean, I really don't know how to talk about generalizing to the population unless you look at the general population.

DR. WATERSON: Ira.

DR. LUBIN: So Greg may provide a counter comment to this,

but I believe it's considered good laboratory practice for the laboratory to establish the prevalence of the variance in their population detected by the test that they use. You know, many, if not most, labs do this, and this is considered a common laboratory practice that gives you an idea of, you know, basically what your population is and whether you're hitting the mark or not.

And, in fact, in California when the state was implementing newborn screening for cystic fibrosis, they actually undertook a fairly extensive evaluation of their population and found that the distribution of CF variants was different than that which was recommended on the ACMG panel. They have a unique population. I'm sure they're not the only ones. But what it caused them to do was to actually reevaluate what mutations they test for with regards to CF and provided then a better newborn screen as a consequence.

So this isn't a novel concept. In fact, it's something that many labs already -- or clinical labs, I should say, already do.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. I might summarize it with document, disclose and explain. In other words, test well and label comprehensively such that the interpretation can be done appropriately, whether it is a different population or is or is not the population to whom that specific customer belongs.

DR. TSONGALIS: So, Ira, I really don't disagree with you because I think it's very important. I mean CF is just one example. We heard earlier from one of the speakers about Tay-Sachs, the mutation spectra being different in different populations, and so I think this is one that has to happen. And it's another one of those things -- I keep trying to think of added value of allowing direct-to-consumer testing, and this is one of those added values that when you're testing that many people, this information hopefully becomes available to everybody, and we get a better view of what's really happening in different populations.

DR. WATERSON: Okay. Any other comments?

DR. MANSFIELD: Thank you. Part (f): Usually case-control studies in published literature provide information about particular markers and corresponding odds ratios. Differences in selection of publications, in approaches for summarizing the information about odds ratios, and in stratifying odds ratios into risk categories that can yield different test results, for example, one approach may report high risk while another reports moderate risk. Is it important to avoid inconsistencies in how the information in the published papers is used?

- And should there be a separate group of experts formed who can summarize information from existing literature?

DR. WATERSON: Okay. Ralph.

DR. D'AGOSTINO: I have a presentation that I do my dog and

pony show with in terms of how do you draw inferences when you don't have a randomized control group, and we sort of rank the different types of data in terms of its usefulness and what have you, and case-control studies are not close to the top. They're very problematic. And do you accept case-control studies for approval solely?

DR. MANSFIELD: Yeah, it depends. We may in some circumstances. If I may clarify? I believe that some of the direct-to-consumer genetic testing companies test for nominally the same risk for future disease; however, the different tests deliver different interpretations of that risk.

DR. D'AGOSTINO: I would think, you know, again, maybe not answering the question, but things like cohort studies -- you can't do randomized control studies obviously, but the cohort studies would tend to have more robustness to them and address some of the concerns. The case-control studies may be very peculiar populations.

Going onto your panel of experts would be hopefully a group of individuals that can sort some of that out, but, you know, we've been sort of dancing around these all along. If you start setting up risk categories according to just case-control results, you really don't know what you're actually doing outside of dividing your group into four equal sets and so forth, and there's really no way out of that. The experts could bring in some judgment on it, but it would be judgment as opposed to real rigor. And I

would agree you should do it, but I think until you get to something like cohort studies, you're not going to be able to sort out some of these issues that you're talking, and even the cohort studies would have difficulties if you have completely different type populations.

DR. WATERSON: Mary.

DR. MAHOWALD: Isn't there the possibility of doing meta-analyses of these different studies? And if there would be that, that would be a group of experts whose contribution would try to --

DR. D'AGOSTINO: The meta-analysis would talk about poolability, I presume, but it would have -- you know, it wouldn't be able to answer the question, are all these case-control studies not typical? It wouldn't -- you know, it would pool what you have.

DR. MAHOWALD: It would be a little closer.

DR. D'AGOSTINO: Well, yeah. I mean, and I think you could start making judgments which studies belong in the meta-analysis versus which don't.

DR. LEE: So this question actually makes me think of Victor McKusick and the work that he's done with OMIM. And if something similar like that could be done for the case-control studies and cohort studies, I think it would be a valuable resource.

DR. WATERSON: That's an excellent suggestion. Any other comments? Okay.

DR. MANSFIELD: This is the final question, part (g). What is an appropriate study design for a direct-to-consumer genetic test that reports absolute risk (or relative risk)? What is an appropriate study design for a direct-to-consumer test that reports likelihood ratios (or odds ratios), or categories such as low, average, or high?

I'll continue and read through the entire question.

- When are prospective studies in the intended use population necessary?
- When using web-based studies, what considerations should be made about possible biases?

DR. WATERSON: I'm going to make you answer all the questions here today, Ralph.

DR. D'AGOSTINO: Should I let somebody else say something first? I'm sorry. I mean, I think the appropriate study of the appropriate type of designs are the cohort studies where you are, in fact, looking at individuals over time, and you know what they were as they entered the study. Those are not going to be always available and some of them -- you know, Framingham's been on for 60 years, and Nurses' Health Study, physician studies and so forth. These are long run studies. If you want to start moving into this arena, have you -- you know, do you have cell lines that you can pull out of something like that and look at more DNA? But, I think that -- you know, to answer your question about the best type of

design, we can't do randomized control, obviously, so a cohort type of study is the best type. But I think we have to, from what I'm hearing -- well, my own understanding and what I'm hearing today is we do have to be willing to look at other databases and sort of get this reproducibility and validation across different studies to give us comfort that what we're seeing in one or two studies is holding up in other studies. And I think we did talk about that we -- I thought the Panel was saying that absolute risk is what we sort of like and then you can break that up into categories.

DR. GALLAGHER: This is Colleen Gallagher. I think one of the issues also is, even though it may be cohort studies and whatever, that some of the protections that people have when research is being done on them in other ways, is to have institutional review boards that have community members and people from different backgrounds and things like that available on those review boards, and I think that sometimes those review boards help in developing the design and asking the right questions to make them rigorous enough. So I would hope that in order to accept those studies that there would be some kind of institutional review board or practice like it.

DR. WATERSON: Thank you.

Kittie.

DR. WYNE: I have a question and maybe I just don't understand this question, but when we look at these tests that are being

proposed for DTC, how many of these tests actually have prospective studies in an intended use population? Do any of them?

DR. MANSFIELD: It is my understanding that most of the studies upon which the results are calculated are from the literature. I do not know how many of those are prospectively performed prior to publication. But if the company wishes to create a new claim and do their own research, we don't know. We're asking would prospective studies be necessary or is there another way to do it?

DR. WYNE: I don't know of a different way to do it other than a prospective study, but I think Colleen's point is very important that if it's done, it's got to be done properly with proper protections in place. But I think that kind of information is important and I think a lot of what we're dealing with right now is we have a lot of information that nobody really knows what to do with, but everybody wants the information and they want to be able to play with it.

DR. WATERSON: Ralph.

DR. D'AGOSTINO: And I think what's happening again, with my own experience, and excuse the biasness of it, is that there are, from NHLBI, National Heart, Lung and Blood Institute, there are a number of cohort studies that do have genetic information and produce very good literature and would be able to give you very sensible answers in terms of very valid answers and lots of reproducibility.

To put a new study together is very formidable, and just one thing, to say again, if you were to mount a study like Framingham or some of these epidemiological studies today, I mean I don't know if you'd ever find the relationship between lipids and heart disease because if anybody has a bad lipid profile, they're immediately put on drugs and they don't develop, thanks be to God, as much cardiovascular disease and what have you. So even putting a new study together and trying to let it run its course, you're not going to get natural history. You're going to get what happens with all of the interventions that's going on today.

DR. HERSCH: Is the question because a consideration may be to require studies of companies before making these available?

DR. MANSFIELD: My clarification will be based on what I believe to be true is that if new claims were to be generated by the company and not derived directly from literature, would prospective studies be required? Could retrospective studies be acceptable in any way?

DR. NETTO: George Netto again. So I have a question. What would be the answer if it was prescription test, directed test, rather than consumer? I would say the same standards. It wouldn't matter that this is a DTC.

DR. MANSFIELD: Yes, you can take the DTC out of it. I believe we're looking for a study design perhaps here.

DR. NETTO: Okay.

DR. WATERSON: Kittie.

DR. WYNE: I guess, then, I would weigh in as saying that would be my dream scenario, that every single one of those SNPs had a prospective study. But remember, I said my dream scenario. But it would be nice as we move forward with all this information to have some kind of prospective data to validate it.

DR. MANSFIELD: Are there concerns about possible bias from web-based studies such as proposed by some of the direct-to-consumer testing companies? Are you familiar with those enough to comment on them?

DR. WATERSON: Kittie.

DR. WYNE: The one comment I would make about web-based studies is it's going to select a certain population. I have a lot of -- well, let's just say I know of a lot of people in Texas who don't have regular access to the Internet, don't use it on a regular basis, and would not be able to sign up to do something like this. So if they did, it would be a major undertaking for them, and so I don't know what the data is, but there's still a high percentage of people in this country who use dial-up modems for Internet access and so that would limit who could actually do these things.

DR. WATERSON: Joann.

DR. BOUGHMAN: Joann Boughman. It would seem to me that no matter how the study is done, the regular standard of peer review is

essential.

DR. WATERSON: Mary.

DR. MAHOWALD: Yeah, I would also be concerned in web-based studies about how to determine the veracity of the study subject.

DR. WATERSON: Are there any other comments?

Any more information that you need, Dr. Gutierrez?

DR. GUTIERREZ: No, I think we're good. Thank you very much.

This has been very helpful.

DR. WATERSON: Does anyone have any closing remarks or final comments they'd like to make before adjourn?

DR. HEJAZI: Yes, I'd just like to make a short comment. One of my takeaways from this Panel is that genomic testing creates complex result, whether this complexity is in the amount of data, the result or suggestion for an action. I think most of us, if not all of us, agree that we need to validate a process for reaching this result. Then the main single question to answer for regulatory path is whether this result will create a safety concern? That's the question, and then according to that, the rest will be determined.

Thanks.

DR. WATERSON: Okay. Go ahead.

DR. NETTO: Yeah, I would just like to thank you all for great presentations. It was really helpful for us. Very helpful.

DR. WATERSON: Dr. Gutierrez, did you have any remarks

you'd like to make in closing?

DR. GUTIERREZ: Sure. Did somebody else?

DR. WATERSON: Go ahead, Margaret.

DR. DAVIS: I just want to thank the FDA for including me in this Panel, and I'd just like to make one comment before I go.

When we're driving in our cars and sometimes our foot gets a little heavy and we're speeding and we see the cop, we kind of slow down and try to do the right thing. So I just want to say for the consumer, the spectra of FDA oversight will hopefully move the for-profit companies to strive upward along the continuum of higher standards for the consumer.

DR. WATERSON: Okay.

DR. GUTIERREZ: In closing, let me just thank everybody on the Panel. Really the discussion has been very, very helpful to the Agency as we move forward to figure out, you know, how we can regulate this direct-to-consumer testing and what makes sense, what risks are there and how do we mitigate the risks. This has been really invaluable to us. Thank you very much.

DR. WATERSON: Thank you. I would like to thank all the presenters and the members of the Panel who were a great help to me and made this a very pleasant, actually, experience to chair this meeting, and I hope you all have a safe trip home.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

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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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