vertical profile test. Less than three percent variation using that particular technique.

And again as you saw earlier, it's in reference to a CDC reference laboratory, their proficiency testing program as well.

DR. WINTER: But is that in reference to the subfractions or to the concentrations of cholesterol in HDL and LDL?

What about those subfractions specifically?

MR. FRENCH: I don't know that there is any data on the subclasses yet. Definitely on total cholesterol, HDL, LDL, VLDL, Lp(a), intermediate density lipoproteins, I believe that's all I can comment on.

DR. GRONOWSKI: That's less than three percent total CV?

MR. FRENCH: Cholesterol, yes,

ma'am, or whoever that was, yes, ma'am.

DR. WINTER: I'm sorry, you still haven't addressed our question about CV for the subfractions. I mean you must know what your reproducibility is for the subfractions.

MR. FRENCH: The only reason why -- I'm referring to her -- is simply because he actually looked at this technique at that level. I am unable to address that actually at the subfractions. But he's indicating to me three percent or less on the subfractions.

DR. ZHANG: I would like to follow up on the three percent CV. What does that exactly mean, if anybody can explain? Three, even HPR is your assay, you will have CV as big as five to 10 percent. Quantity of your assay, you have three percent CV? Are you sure? This goes to the public record, okay?

DR. OTVOS: Yes, as far as the NMR

assay, I think Parvin Waymack showed a table from a published, recently published study, that showed the results of blind duplications, 20 blind duplicates, and two pools. And not surprisingly the coefficients of variation are better for the pooled subfractions, so total LDL particle number, less than five percent CV, the individual subfractions greater than that, but generally less than 10 percent Cvs.

The data is available. The other question about standardization, what is done is to use frozen pools of serum as day-to-day standardization or for quality control material.

And the way that the NMR data is referenced in terms of absolute concentrations is with a chemical reference standard that is measured everyday, so every one of the 15 machines is able to be put into essentially very good calibration.

And as I mentioned, as part of

our quarterly proficiency testing, the data on all 15 of these machines is compared, and the agreement is very good.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: Just sort of a follow up question. And maybe the industry people could answer this.

These assays are run I believe maybe just the one lab, with the possible exception of the electrophoresis. And I know the reproducibility of the NMR and the VAP are very very good.

But the question would be, I mean will they just always continue to be run like that? At one time Dr. Otvos I think was talking about other machines that would be all over the country, or might one anticipate that the reproducibility would be poorer if they were being run in routine labs? How would that work?

DR. STEELE: Dr. Gutierrez?

DR. GUTIERREZ: I would like to --

I am not sure that this is going to a place that we are either comfortable with or will be helpful.

The reproducibility, whether -- when someone comes into it, would be looked at. That would be part of our assessment.

We don't necessarily have all the companies here. Not everybody is able to attend it, so I'm not sure it's going to help you that much.

We would usually look at lab to lab and that kind of thing when we look at it. So I think it's good to have an idea roughly what they have, but I'm not sure if we go into specifics that it's going to help us.

DR. STEELE: Any more questions or comments, thoughts?

Dr. Winter?

DR. WINTER: I'd like to make one comment. And that is, there was a paper I think published in 2003 in JAMA that looked

at cumulative or what proportion of coronary heart disease was due to identified risk factors, and what proportion of coronary heart disease was identify -- was not identified as to traditional risk factors.

And I know that I was taught up through the `80s and `90s that half of heart disease at the time had no identified risk factors.

And then this new analysis was done and published in JAMA about 2003, and somewhere between 90 and 95 percent of risk factors were really explained -- development of coronary heart disease.

So if we ask do we have the right LDL cutoff, with the right number of risk factors, and is that appropriate in NCEP, maybe that will be revised as Dr. Remaley said in the future.

But again, I would say that if somebody comes in and has one established risk factor and normal lipids, to say that

the normal lipids, they weren't informative to us, I don't know that they would ever be informative.

In other words, I think in some ways the panel is looking for an explanation for all heart disease by there being some kind of ultimate answer in lipids, and I think there will be patients that don't have any lipid abnormalities and yet get heart disease because of other risk factors.

DR. STEELE: All right. Okay, we are going to move on, since the panel has no more general questions or comments, we will proceed to the second open public hearing of this meeting.

OPEN PUBLIC HEARING

DR. STEELE: We have four speakers scheduled for this session. As before, each speaker has been allotted a maximum of seven minutes to present their views.

For the benefit of the speakers who may not have been in attendance during

the first open public hearing, I will reread the open public hearing disclosure statement.

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 the meeting.

Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such 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.

The four speakers for this afternoon will be Dr. Cromwell, Dr. Schilling, Dr. Ziajka, and Dr. Naito.

We will begin with Dr. William Cromwell. And please, panel, we'll hold all questions like before until the end of the presentations. And there will be time for questions at that time.

DR. CROMWELL: Good afternoon.

My name is Dr. William Cromwell. As indicated, I am the director of the division of blood and protein disorders at

the Presbyterian Center for Preventive Cardiology in Charlotte. Also serve on the faculty of Wake Forest University.

By way of disclosure my travel and lodging has been paid by LipoScience, and I'm also a consultant for LipoScience.

The topic I'd like to address is the clinical utilization of lipoprotein subfractions. A chapter relevant to this subject was submitted to the panel for its consideration that has been accepted in an upcoming textbook entitled Therapeutic Lipidology.

Let me begin with a case, because we all see patients, and that's really what this begins to gravitate to. So a 42-year-old male who was sent to me for screening evaluation, not because of a history of dyslipidemia or coronary disease, but because of major risk factors, in this case, family history of a father who had experienced a non-fatal MI at the age of 50,

and died of an MI at the age of 65, and a brother who experienced a nonfatal MI at the age of 45.

Beyond that history he presents on medication for gastroesophageal reflux. He's also taking aspirin. Family history is as noted. His review of systems is unremarkable. Six foot two, 203 pounds, and he does not have a 40-inch waist.

What he does have is a lipid profile, total cholesterol 146, LDL cholesterol 94, HDL cholesterol 24, triglyceride 142.

The NCEP's recommendation for this individual since he has two risk factors is that he needs to undergo a Framingham risk calculation to assess his degree of risk which, not unexpectedly because of his age, turns out to be only one percent.

His LDL cholesterol target, by current recommendations, would be less than

130, and he is certainly there.

In the six minutes or so we have to see patients, though, we have a few other considerations. He does not meet criteria for metabolic syndrome. He has what would phenotypically be described as isolated low HDL cholesterol.

Now of interest to me as a clinician are three questions.

Number one, do I believe there to be lipoprotein risk present given that lipid profile? And the answer is, yes, at least HDL cholesterol we know to be a major independent risk factor if it's low, and at that level of Hdl cholesterol which jump out of the page as being problematic to us.

Is there anything beyond that is an open question.

Number two is, I think part of the discussion I was hearing this morning was the origin or the source of lipoprotein risk. There are many things that overlap

and have high intercorrelations, for example size and number that we will talk about in just a moment.

So understanding clearly where the source of risk emanates from has a great deal to do with what we as clinicians should value in what we manage in a patient.

And then number three, what are the lipoprotein goals of treating this individual?

Well, to move from here into a discussion of where risk emanates from, you have heard a lot about science today. And we've known for a long time that there are associations of small size -- this is a review article that I wrote back in 2004. At that time there were 17 cross-sectional epidemiologic, 8 prospective epidemiologic, now 7 clinical intervention trials, that have looked at the association of size with risk.

As you know small size does not

exist in a vacuum. It's part of a large path of physiology intertwined most commonly with high triglyceride, low HDL cholesterol, and increased numbers of LDL particles, as well as clinical sequella, such as diabetes, metabolic syndrome, and insulin resistance.

And what that requires you to do then is to handle interrelationships and intercorrelations as you heard with MESA data earlier today.

And when one adjusts for these relationships, what you find is that size as a quality frequently does not predict coronary disease once you adjust for such things as high triglyceride, low HDL cholesterol, increased particle number.

So the question would then be, what about particle number? Do the number of LDL particles, not size, have the same fate, or would they hold up to more robust scrutiny?

And this is where I think the

panel may need some sensitivity is the idea that numbers of particles and size of particles are two different parameters.

If we look at numbers of particles, here assessed by NRM, LDL particle number versus LDL cholesterol, there are a number of outcome studies which have examined the relationship of particle number by NMR and LDL cholesterol with respect to strength of association even after multivariant adjustment, and I'll point out that VA Hit (phonetic) obviously is a well known intervention trial in which there is on trial treatment to data with respect to what is the value of knowing numbers of particles versus cholesterol.

And in all of these you will notice that there is significantly stronger association of risk of numbers of particles versus LDL cholesterol, after accounting for HDL cholesterol, triglyceride, and many other confounding features.

So having said that, the question would then be, how do we account for LDL quantity? Most commonly we account for LDL quantity by LDL cholesterol. The problem is, the amount of cholesterol carried per particle is highly variable, and as a result, knowing LDL cholesterol does not tell you the number of particles.

This is most problematic in certain paths of physiology, such as metabolic syndrome and type II diabetes. Shown here are data which were published in January in Circulation looking at the two alternate measures of LDL quantity, LDL cholesterol in the hatched marks, and LDL particle number in dark.

The X axis are the different criteria for the metabolic syndrome. And as you know three or more of the defined criteria, which define the presence of the metabolic syndrome.

Here you see the quantity of the

LDL cholesterol appears to be very flat, not very elevated, and not changing as a function of criteria for metabolic syndrome.

Unfortunately, that does not reflect the true quantity of LDL present, because the number of particles show a very strong rated relationship, and indeed, there is significant LDL excess without having a significant change in LDL cholesterol.

To understand the magnitude of that, it's important to look at population equivalent cut points. If you look at Framingham, our current NCEP guidelines of 100, 130, 160, LDL cholesterol, emanate from the 20^{th}, 50^{th}, and 80^{th} percentile of the Framingham population.

By direct extension in the MESA population the 20^{th} percentile is an LDL particle number of 1,000; the 50^{th} percentile is LDL particle number of 1,300; the 80^{th} percentile LDL particle number is 1,600.

And this allows us to understand

how frequently you find discordance of particle number and LDL cholesterol as well as the clinical implications of that discordance.

If we take a look back at the question of Framingham metabolic syndrome, and ask what does the histogram of particle number look like when LDL cholesterol was below the 20^{th} percentile, below 100, you find the particle numbers highly heterogeneous, with only 23 percent of individuals having the expected low number of particles, 75 percent of individuals having some magnitude of particle excess, the degree to which can be quite high indeed.

So if the problem is LDL particle concentration excess has a strong association with outcome behavior, then there is a consequence to having a lot of particles.

Do we see this in other

problematic populations like type II diabetes? These are data that are generated from AJC, which was published this week. And again what you see in 2,300 type II diabetics, 900 of them have an LDL cholesterol less than 70 --

DR. STEELE: Can you wrap it up?

DR. CROMWELL: Absolutely.

You will see that 40 percent of individuals have a particle number above the 20^{th} percentile, when LDL cholesterol is below 70. And the MESA population, if you take people who have an LDL cholesterol below the 20^{th} percentile, 100, they have a divergent number of particles.

And what's interesting is that the first quartile for particle number, given the same LDL cholesterol, has a much lower IMT association than a higher number of particles. The more particles, the more the association.

So here is our case, and this is

my last slide, and the question is, is lipoprotein risk present? What is the source of that risk? And what are the goals of therapy?

LDL is bad. A lot of LDL is real bad. And this person has a lot of LDL which is missed by an LDL cholesterol of 94, but a particle number which is above the 75th percentile at 1,800 nanomoles per liter.

Thank you.

DR. STEELE: Thank you.

Our next speaker? Ms. Schilling? No? We'll move on then to our next speaker after that, Dr. Ziajka -- sorry if I mispronounced that.

DR. ZIAJKA: Good afternoon. I'm Paul Ziajka. I've run a private practice lipid clinic in central Florida since 1987.

By way of disclosure I guess I am for the last two years have been the part-time chief medical officer to Atherotech. But I am really going to limit my comments

from the perspective of a private practitioner who does this everyday seeing patients.

You know if you ask yourself what we do, what is the use of a lipid panel, why do we screen for lipids, well, I mean theoretically there are two answers to that.

One is to identify risk in somebody who looks relatively normal, and that, then, if that risk is identified, to possibly direct treatment.

A lot of discussion centered this morning around the fact that the traditional lipid profile identifies about 50 percent of the risk in a high-risk population. And if you are using that as a screening test it's not very good. I mean we could save the health care industry a lot of money by replacing a lipid profile with a flip of the coin. Because that gets about a 50 percent chance of identifying somebody with premature risk as well.

I think it was Dr. Warnick presented the data, and it's been repeated several times, that if you do an advanced lipid profile that includes LDL particle size or density or number, HDL subtypes, you can improve that sensitivity from 50 percent to about 85 to 90 percent, into a realm where risk factor screening I believe is worthwhile.

And there is tremendous data -- Bill commented on it -- the question was asked earlier about prospective studies. There are a number of prospective studies involving things like LDL particle sizes. The Quebec cardiovascular study, people with small dense LDL who were normal at baseline, without any disease, at the end of that study, if your LDL was smaller and denser, they had a four times in having a premature event.

Similar data for the HDL subtypes, and certainly an overwhelming

amount of data for Lp(a) and remnant lipoproteins.

One other thing that wasn't discussed very much is the issue of using this data to direct patient care.

One of the very earliest speakers talked about personalized medicine. And you can do that now with advanced lipid profile. Response to diet. Type B people, people with small dense LDL, respond much better to LDL lowering in dietary therapy. Those are the people that my dietician will spend a lot of time with. Everybody sees a dietician, but much more intensive intervention in people with pattern B.

The statins are very different. The rationale for selecting drug therapy should not be which rep has been in your office last, or how many samples you've got in the storeroom. The stains have got different effects in LDL particle size, on HDL subtypes, on things like Lp(a).

So I want to wrap it up. I'm just saying, number one, as we're screening for risk the traditional lipid profile does not work very well. An overwhelming body of data suggests that advanced lipid parameters can almost double your ability to identify premature risk.

Number two, that data does have some implications for therapy.

And just the last thing I want to close with, there was a lot of talk this morning also about allowing the use of these advanced lipid parameters. And I think the panel needs to keep in mind that they are being used extensively now. I mean the VAP alone, which I'm most familiar with, have 1.2 million tests ordered last year. So the issue is not whether the FDA is going to allow the use, but how it's going to be regulated and standardized.

And I thank you for your attention.

DR. STEELE: Thank you.

Our last speak is Dr. Naito.

DR. NAITO: Good afternoon.

My name is Herb Naito. I'm from NorthStar Consulting Service. I am a scientific adviser to Atherotech, Inc. I have no other affiliations with any other manufacturer.

I would like to first thank the panel for inviting me here to share my thoughts with you today on the origin of risk factors, primarily, why we should measure and on whom.

The data I'm going to present to you is old. It's over 25 years old. And I say that to you in confidence that the methods that we used back then were very laborious; the preparative (phonetic) ultracentrifuge, the classical technique, one of the tools that used to define lipoprotein. So I believe that the accuracy of the data we generated does reflect in

fact the patient population.

This patient study, the problem first emerged from the cardiologists saying that, are the values on the standard profile accurate.

And I responded by saying that we are one of the seven reference laboratories standardized by the NHLVI CDC. And therefore I was confident to stand behind the values.

They said that for a third of their patients had a normal lipid profile. I said from our basic research studies, it is clear that each of these major lipoprotein classes are heterogeneous. Maybe if we tease it apart further we might have better correlation. And this I will share with you.

A brief background, I think we had a major step forward with the NECP guidelines. By increasing the clinical usefulness of total cholesterol measurement,

by partitioning the measurements into lipoprotein components.

Furthermore, recent studies have shown that by partitioning these major lipoprotein components into subclasses, as well as lipoprotein little a, lipoprotein density, particle size, apolipoproteins, further enhanced their association with disease process.

The NCEP III guidelines further identified the emerging risk factors for further assessment of CAD risk.

And lastly there has been a tremendous improvement in technological advancements of these analytical procedures that makes it very readily available with a tremendous amount of precision, reliability, and costs have lowered substantially and with a quick turnaround time.

Those of you who have been involved with the classical method that took us five to seven days to separate the

fraction, purify them, and then measure the lipid components.

So the question I'd like to present to you is, does the partition of the major lipoprotein components show better association with the disease process than the standard lipid panel?

And furthermore, if we're going to use this as a diagnostic test, does partitioning of the major lipoprotein components show better predictability of the disease than the standard lipid components?

This is a small double blind study, 226 male subjects at the Cleveland Clinic Foundation, with a mean age of 52 years, who had some angiography performed.

Twenty-six standardized sites were evaluated by two cardiologists for the degree of obstruction, and the mean scores were tabulated. The most severely occluded coronary stenosis score was used for simplicity to categorize each of the

patient's severity of disease, and placed into one of four categories.

The first group would be the control group. Second group, one to 50 percent occlusion. The third group, 51 to 99 percent occlusion. And the fourth group, severely occluded group, 100 percent occlusion.

The data was analyzed for analysis of variants and covariants as well as correlation analysis.

And you can see that the first five constituents were not significant. When we compared the mean values among the four groups, people at A-2 became significant, but the subfraction, HDL-2, to equal A-1 equal B were highly significant.

And if you look at it from the statistical standpoint of correlation coefficient, as it goes down the slide, you can see increasing degree of probability that the first four were not statistically

significant, and it increases from that point on whereby the HDL total cholesterol, the LDL, the Apo B, et cetera, were highly significant, ending with the HDL-2 as well as the ratios of HDL over HDL-3 being very, very significant.

In another study, we teased that original study apart to see whether there is any predictability of these biomarkers. And we used the Receiver Operating Characteristic Curve, something that is very little done, basic research or clinical research in this field.

But we're looking for increases in sensitivity and specificity of a test, and then be able to predict the predicted value.

The sensitivity, the probability, given the presence of CAD or the disease, the abnormal test results indicate the presence of the disease, and its specificity being probability that, given the absence of

the disease, the test results exclude the disease.

When you do this you can get the best cut point to use to get the best sensitivity specificity. And as you go down the slide you can see that the sensitivity specificity increases whereby the Apo B ratio, the HDL subfractions, were highly sensitive in terms of sensitivity and specificity.

This in summary, then, the cineangiographic study demonstrates that when you partition the measurement of the major classes of lipoprotein, into the subfractions, the Apo lipoprotein components can in fact enhance the correlation with the increasing degree of coronary artery occlusion better than the standard lipid profile, and the enhanced prediction of the severity of the coronary artery disease can be achieved with a greater sensitivity and specificity than the standard lipid profile.

My recommendation to the panel is the clinical use of the emergent risk factors should not be used with generalized screening. They should be targeted selectively for a better estimate of the absolute risk for CAD, and the high risk patient be defined as symptomatic patients with documented CAD, who have CABG or stent implant, or with abnormal lipid profile, or the asymptomatic patient with positive history for premature CHD, and with normal lipid profile; and finally, patients with diabetes, or metabolic syndrome.

In addition the use of emergent risk factors should be encouraged for basic and clinical research.

And finally every effort should be made to develop standardization programs to help ensure the accuracy of testing of these advanced analytical techniques.

And I'll close by saying on an individual basis, nearly half of the MI

patients have normal lipid profile. Doing a standard lipid panel does not provide an accurate view for HDL risk assessment for many patients. Using the emergent risk factors provide a more comprehensive estimate of absolute risk. As an example, Superko et al showed that simply adding LDL subclasses increases a diagnostic yield from 55 percent to 84 percent for subclinical CAD in asymptomatic patients.

The analytical technology is available, ready to do the emerging risk factors. Its selected use should not be denied.

DR. STEELE: Thank you.

We are now going to give Dr. Muniz an opportunity to address a question that was brought up this morning in which he has some information to share with us.

DR. MUNIZ: I truly appreciate the opportunity to make this statement for the panel.

DR. STEELE: We'll have five minutes.

DR. MUNIZ: I'll try to make it brief.

During this morning's presentations, an article by Ensign was referred to over and over and over again. And I thought I had to make this clarification with regard to that study, since it's already -- some of the panelists have brought it -- the question about the study itself.

It refers to a study done with 40 patient samples, showing how these methods all are in complete disarray when comparing one method to another.

I just want to say that the method that I represent is the two gel electrophoresis method, and the author of this paper never used the test as was recommended by the manufacturer.

In the article he says that two

gel elecetrophoresis method, uses LDL score. Number one. Number two, it indicates that the method recommends that the patients be classified as type A, intermediate, and B, which is not a recommendation.

Number three, it indicates that we use cutoffs of 255 and 265 to make that differentiation, which is not correct either.

So the point that I'm trying to make is that the weight of this article, even though it has been mentioned over and over, I think needs to be clearly investigated, and all these points should be brought to the attention of the panel.

All these criteria are the creation of the author of the study, not the recommendations of the test as it's properly used.

Thank you very much.

DR. STEELE: Thank you.

Is there anybody from the

audience that would like to make a comment? We'll open it up for some brief comments.

Anybody new? Okay, and then finally I'm going to make a call again for Elizabeth Schilling? Is she in the room? She had asked to speak here.

Does the panel have any questions for the open public hearing presenters?

Dr. Tsai.

DR. TSAI: I just have one question for Dr. Cromwell.

You mentioned that, Dr. Cromwell, you mentioned that the use of these lipid profiles can lead to differential therapy. You primarily talked about, I think, the so-called B pattern that you would emphasize the use of diet.

By that do you mean that the diet would lead to perhaps lower triglyceride, and therefore, is it also your recommendation that sometimes you would preferentially use fenofibrate?

I mean what do you mean? Could you clarify this a little bit for me?

DR. CROMWELL: I'll give you a response. I think Dr. Ziajka actually made that point in his talk.

But as a clinician, yes, I think that lipoprotein can help me uniquely change patient management.

The way I look at the data is, what do we have most confidence in at an outcome level that has value that needs to be addressed and managed?

The data as I understand it, and as we've talked about it today, handled in a multivariant fashion so that intercorrelations are taken care of is numbers of LDL particles.

When LDL particle number remains high despite reasonable LDL cholesterol, that person is a candidate for a different therapy. More LDL reduction; it's interesting that combination therapy, statin

plus niacin, statin plus fibrates, have a unique effect in people who have small LDL in that as they affect triglyceride metabolism, the numbers of LDL particles are actually reduced to a greater degree than is reflected in LDL cholesterol. And as a result the change in LDL cholesterol does not properly account for the amount of LDL which is present; it does not properly account for the response to therapy.

So I think the question is, if it matters the quantity of LDL, then that is the way -- and these therapies can be uniquely identified.

Now diet also, to Paul's point, has a much more significant impact in metabolic syndrome insulin resistant patients than it does in say the FH patient population.

DR. TSIA: Basically what I'm trying to lead into is diet, or use of fibrate, probably directly lowering

triglyceride, no?

DR. CROMWELL: The effect on the composite dyslipoproteinemia is how I would characterize it, because it is a composite just like a proteinemia that has lipid phenotypic characteristics, the composite being increased numbers of LDL particles, increased numbers of small particles, triglyceride is often up, HDL cholesterol is often down.

The effect of diet and medications again in my way of thinking should be directed not only to the lipid disorder, the LDL cholesterol, HDL cholesterol, triglyceride, but also the unique value of what do you do when you encounter LDL particle excess. You deploy your therapies in a uniquely directed way for the patient to address that.

DR. TSIA: Thank you.

DR. STEELE: Yes, Dr. Granowski.

DR. GRONOWSKI: So you then lower

that patient's small LDL, you increase their larger LDL, does that -- do you have evidence that that changes their outcome?

DR. CROMWELL: I would be more concerned with their total number of LDL, not their small or large.

DR. GRONOWSKI: I stand corrected, the particle number.

DR. CROMWELL: It's an easy mistake to make, because those things are roughly overlapping.

But if we look at VA Hit as a good example, they are on trial various parameters, LDL cholesterol, non-HDL cholesterol, LDL particle number by NMR, looking on trial, only LDL particle number by NMR was significantly associated with prospective risk.

Same thing was true with HDL particle number versus Apo A-1 and HDL cholesterol. HDL particle number strongly associated with future risk.

And so yes, the value on trial, on trial predictive value in that is established.

DR. STEELE: Just a second here, you are excused, sir.

Go ahead, Dr. Watson.

DR. WATSON: I had another question for Dr. Cromwell.

So in this individual your example of CG was a strikingly positive family history of premature coronary disease, and a strikingly low HDL, that's a patient that I would do statin and combination therapy off of that.

And I'm not sure that advanced lipoprotein testing would alter my therapy. I think the best clinical trial data we have suggests that doing that would be the right thing for him.

Would you disagree with that?

DR. CROMWELL: I think as a starting point I would agree with you that

this very high risk individual with low HDL cholesterol could certainly benefit from combination therapy. So it's not a question of treat-no treat. I think it's a question of asking, what source of risks are present. Is it HDL in isolation? Is it LDL and HDL quantity that we're dealing with?

And how do I judge the effectiveness of the therapy which he is a good candidate for? If I use statin combination therapy with that individual, and I'm trying to raise his HDL and his LDL cholesterol was not significantly elevated to begin with, when I get to an LDL cholesterol of 70 to 80, should I be satisfied that he's had adequate LDL reduction?

The problem there is the data that I showed in which people can have a very low LDL cholesterol and highly heterogeneous numbers of LDL particles.

So the question of whether this

person has had adequate LDL reduction is a function of how many particles are present. If the person's LDL cholesterol has been rendered reasonable but the particle number has not, then that is a person for whom more aggressive therapy I think should be entertained, versus an individual who started on the therapy, combination therapy, for the appropriate clinical indication, the question is, if LDL cholesterol, pick a number, had they had adequate LDL reduction.

DR. GRONOWSKI: Have there been any clinical interventional trials with prespecified outcomes and looking specifically at particle number showing improve outcomes?

DR. CROMWELL: Good question. Short answer is, one old, and then I would add a caveat for statin trials.

DR. GRONOWSKI: But those were not prespecified outcomes?

DR. CROMWELL: In the FATS trial

people were selected on the basis of particle number, not LDL cholesterol, with known coronary disease, followed prospectively. There was a placebo group, there were two interventions, cholestyramine niacin, cholestyramine instatin. The prespecified hypothesis were angiographic correction in clinical events.

The outcomes were that the placebo group had significant angiographic progression and increased events; significant reduction in angiographic progression and decreased events in the treatment groups, with the most striking on trial predicter being numbers of particles.

Also if you look at statin trials, AFCAP TEXCAP, I think our problem with statin trials is that these are trials designed to test the effect of medications, not the effect of achieving biomarker targets of therapy.

As people swallow statins they

have fewer events. But the question is, what values on trial are most predictive of the benefit which is observed. And AFCAP TEXCAP, it was not LDL cholesterol; it was numbers of LDL particles.

So what we are left with are a group of data that have been operationalized into the NCEP guidelines and justly so, that LDL quantity matters. But the outcome studies that have been dealt to us for inspection are those in which the primary hypothesis is, does swallowing the pill make a difference? And having made a difference, you are left in a lurch to try to understand on trial predictive value until you go through these types of exercises.

DR. STEELE: Dr. Grines.

DR. GRINES: I guess I'd like to ask Dr. Watson why she would treat that case CG. I mean I understand he's high risk because of his family history, but he's well within the guidelines. I mean you are

talking about primary prevention, and the guidelines would state an LDL of less than 130 is appropriate for him. So he starts at an LDL of 94, and this is exactly the case that personally I would question how to treat this patient.

DR. WATSON: It the NCEP guidelines it does make a very strong case for looking at individuals who have a predominant striking risk factor and treating them based on clinical guidelines, not necessarily following just their strict guidelines, but if you have a single really strong risk factor, then using your own clinical judgment. And this individual has two single really strong risk factors. So I think he would fall outside of the standard LDL of less than 130 as what he needs.

DR. STEELE: Yes.

DR. SHAMBUREK: I don't really want to dwell on a single patient or the inadequacies of the guidelines, which will

miss, as we know, isolated low HDL. The question really to you would be, as a general one, did you measure just Apo B levels, and would Apo B have picked up a decrease or an increase particle in this patient, you know, without the other test.

DR.CROMWELL: Apo B is another measure of LDL particle number. As you know it's strongly correlated with LDL particle number by NMR, so those are two ways in which you could assess LDL particle number.

DR. MARCOVINA: Wouldn't you say that there could be primary measurement of LDL particle, or Apo B containing lipoprotein particles. It's the primary measurement, is the one used for 20 years. So it's not an additional.

DR. CROMWELL: I'm sorry, I misunderstood.

DR. MARCOVINA: I said Apo B, at this point in time, gives us the possibility to measure directly the HDL particle number.

It's a good indicator.

DR. CROMWELL: I wouldn't disagree. Sorry if I misspoke. I agree.

DR. STEELE: Dr. Watson.

DR. WATSON: I would just like to echo what Santica has just said. I think Apo B is well -- I mean it's very commonly done in clinical practice, and it's a very good marker of particle number.

DR. GRINES: Can you trust the result though? Or are there still a lot of issues with measurement of Apolipo proteins?

DR. WATSON: I think Apo B is actually a very good test, and it's actually in some ways more reliable than lipoprotein measures of LDL.

DR. LEVINSON: Could I address that? I mean I think that statistically you can't really tell a difference between one HDL cholesterol and Apo B anyhow.

Statistically you really can't tell the difference between, once you start

adding other factors, between Apo B and HDL cholesterol. And though there could be some individual differences, you know, a statistical analysis won't really show any large difference. And there has been at least three papers in the last two years showing that. I think one paper, Ridka and associates showed that in women, actually they came to the conclusion that non-HDL cholesterol was better than Apo B. And then in men it was shown Apo B was better than non-HDL cholesterol.

But in all these papers they used all kinds of statistical manipulations to show some kind of a very little difference. So.

DR. STEELE: Go ahead.

DR. MARCOVINA: If this is the case, and the value of Apo B is practically nonexistent, if you take into consideration the non-HDL cholesterol, then that would make the case also for determining the HDL

particle number by any other method; is that correct? Okay.

DR. STEELE: All right, at this time we've been informed that Elizabeth Schilling is here, and we will have her give her presentation which will be seven minutes.

Okay, I have to read this. The open public hearing disclosure statement.

Both the FDA and the 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 sessions of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

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Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Ms. Schilling.

MS. SCHILLING: Thank you.

Good afternoon, and thank you for allowing me to speak today about the benefits of using lipoprotein subfractionation in a clinical setting.

For financial disclosure, I have no ongoing financial relationship with Atherotech, which is the company that I use most frequently for advanced lipoprotein analysis.

I am on their speakers' bureau and do receive honoraria for occasional educational programs, averaging one to two times a year for the last four or five years.

I am on speakers bureaus for pharmaceutical companies, for several of the statins, but that should not affect this presentation.

My current role is the director of preventive cardiology programs at the University of Maryland Medical Center, where I've practiced for the last 3-1/2 years.

Prior to this I organized two other lipid clinics, one in a primary care setting, one in cardiology, for the purpose of advanced cardiovascular risk production.

And all three settings, the utilization of particle subfractionation was vital to the success of individualized patient treatments.

I'm confident that the science behind particle subfractionation has been presented, so I'm just going to focus on the clinical application.

My practice is based on the premise that patients are self-determined beings, and that my job is to provide them with enough information that they can make well informed good decisions about their own health care. It's not my job to just simply dictate what they should take and what they should not take.

I firmly believe that informed patients are much more likely to comply with prescribed therapy. And my goal is not simply to lower their cholesterol numbers, but to really look and treat all aspects of cardiovascular risk.

As cardiovascular disease is not a disease of the lumen but of the endothelium, my focus on patient care is to reduce endothelium inflammation through individualized assessment and intervention.

In 2002 I analyzed data from 991 consecutive patients that had the Atherotech VAP test. The population was from two distinctly different categories of patients, one in a very affluent area, another on the rural Eastern shore; 77 percent were from the affluent area; 60 percent were men; 49 percent -- 49.3 percent were female.

What I found was that 75.9 had LDLs greater than 130; 77.9 had low HDLs less than 40; 2.6 percent had triglycerides greater than 500; 28.5 percent of this random population had Lp(a) greater than 10; IEL greater than -- excuse me, IEL greater than 20, 45.6; 60.8 percent did have small dense LDL, and 40.6 percent had isolated low HDL.

Among women with HDL levels greater than 40 63 percent had HDL-2 levels that were low.

So they appeared top have adequate HDL protection, but in essence, more than half really did not have adequate anti-inflammatory properties of the HDL.

But the most starling finding that I found was that 68 percent of each population regardless of their affluence had criteria to meet metabolic syndrome that would not have been picked up if we didn't look at subparticle fractionation.

So in clinical practice I evaluate for all risk factors and explain to the patient how each of these risk factors may affect their health.

With the test results in hand, I use a diagram of advanced lipoproteins with the subfractionation and explain to them each of those different disorders and how it relates -- how to relate it to their

lifestyle, for example, with small LDL, whether or not the triglycerides are involved, or what other risk factors. But I use that so the patient can understand. The patient does receive a copy of these results. We agree upon a mutually decided program, and we reevaluate using the advanced lipoprotein subfractionation.

I am continuously amazed at how many patients become compliant when they start to see the particle size change. They actually come in eager to know if they have improved.

I give them all the data I can possibly give them so that they can understand why improving particle number, particle size, makes a difference in overall health.

I can fine tune their pharmacological therapies, use less drug. Most of the time diet therapy makes a huge difference.

When I first started back in preventive cardiology in 1996 I was working in a cardiovascular office, and the LTAP data became available. And I couldn't believe that only 18 percent of patients with LDLs -- that 18 percent of CID patients had LDLs below 100. So I repeated the study grabbing 200 charts from our cardiology office of patients known with coronary disease. And we were better, we were at 22 percent.

And that's what I used to start my lipid clinic. A year later, using the subfractionated matt test, my goal -- I was able to treat 83 percent of those CID patients to goal.

And again I believe that using subfractionation is what helped inspire the patient to become more compliant.

Have I done outcome studies showing that it's made a difference in their cardiovascular death rate or morbidity rate?

No. But to me it's abundantly evident that after a decade of lipid interventions and trials, that still more than 60 percent of patients on statin therapy still go on to have events or an MI.

And simply going beyond simple healthy lowering in my opinion it's the only path to success.

Thank you.

DR. STEELE: Thank you.

Again, we're opening up the question from the panel, for her or for anybody who spoke before.

Dr. Winter.

DR. WINTER: Ms. Schilling, did I hear you correct to say that 68 percent of the patients had the metabolic syndrome.

MS. SCHILLING: That's correct.

DR. WINTER: But you would only have recognized that because of the Atherotech?

MS. SCHILLING: With the small

dense LDL I was able to look at their particle density. I did not have information on their weight or their blood pressure. But simply looking at their test result I was able to come up with that.

They may not have had triglyceride issues or low HDL, but 68 percent by those numbers alone, through those test results alone.

DR. WINTER: But does that validate the test? Since the patient is seen by the clinician and would know the BMI?

MS. SCHILLING: No, I'm just saying for information that when you look oat public averages of metabolic syndrome it's always been in the 30 to 40 percent range, and I was amazed that it was so much higher despite the socioeconomic status.

DR. WINTER: And then did you go back and look at the clinical charts?

MS. SCHILLING: Oh, yes.

DR. WINTER: So of those 68 percent, did all of those patients have elevated BMI?

MS. SCHILLING: No.

DR. WINTER: Or you had normal weight metabolic syndrome patients?

MS. SCHILLING: Absolutely. I can't give you a percentage, because I did not chart that down. But yes, there were plenty of patients who were normal weight, norm tensive.

DR. STEELE: Dr. Tsia?

DR. TSIA: I'm confused. Are you redefining metabolic syndrome?

MS. SCHILLING: No.

DR. TSIA: I'm just confused about what you are saying. You're saying, they have metabolic syndrome?

MS. SCHILLING: I'm saying based on the clinical data, based on a lab test, they either had the three components that should indicate metabolic syndrome. Without

the weight or the blood pressure I looked at low HDLs, triglycerides and small dense LDL.

DR. TSIA: You're saying there's a correlation.

MS. SCHILLING: Correct.

DR. TSIA: You're not trying to say that you found a new definition for metabolic syndrome.

MS. SCHILLING: That's correct.

DR. TSIA: It's a little confusing.

MS. SCHILLING: I'm sorry.

DR. STEELE: Any other comments or questions? Oh excuse me.

DR. ZHANG: Just to follow up Dr. Tsia's question, do you think these inflammatory markers were bring the changes in terms of diagnostic practice and the criteria in the clinic, based on your --

MS. SCHILLING: Yes, in my observation, yes, I do. I think it changes the aggressiveness of therapy. I think that

be showing the patient and/or the clinician that may refer the patient to me all the subfractionations that they are more likely to be compliant based on knowing the data and then following it subsequently that we see a change with simple interventions; we can document the change and show improvement.

I also use another test looking for inflammatory markers. And you can see based on -- I'm not going to say for sure that that's what it is; I'm not going to say that -- but I can also see those inflammatory scores improving.

DR. ZHANG: I think my question was more direct. What do you think -- we already heard or reviewed a lot about this type of assay. And do you think this is a stage to make an assumption such an assay will make an impact on clinical practice?

MS. SCHILLING: My simple answer would be yes, it's time. And I wish I could

just say, show you the experience that I've had using these over the years, but yes, it does make a different.

DR. ZHANG: Okay, if this is the case, what is your opinion in terms of how to standardize and how to really improve the clinical practice, such assay, just in theory, don't have to particularly say which method is good or bad.

In your opinion as a clinician what kind of idea you have, if such an assay were to impact clinical diagnosis and treatment.

MS. SCHILLING: I would start by doing more assessment of cardiovascular risk, not just looking at an LDL number, but looking at the total patient. And I find that the patients that are referred to me don't have that.

When I see these patients and make recommendations based on the numbers, I'm teaching the referring provider how to

further look for risk.

So using the small LDL or the other advanced lipoprotein subfractionations, it's very helpful for other clinicians to see how to assess for risk.

How to disseminate that to a larger population, I'm not sure. But I know that I'm asked every semester to speak to the medicine students, the medical students at University of Maryland on how to evaluate this, and their eyes are open because they never heard anything about further than the routine LDL.

And every time I said that in their clinical practice, and I do a clinical rotation three times a year with fourth year medical students on an elective for physical activity and nutrition. And when they look at -- and I only use the VAP test -- when they look at the VAP test and they see that in correlation with their lifestyle, it's

like a light bulb goes off, and they are able to understand better why somebody's diet makes a huge difference on their LDL subfractions, and they are able to just -- rather than just say, follow a low-fat diet, and I'll see you in six years, they actually give them better diets based on that. In my experience the Mediterranean style diet has been much more effective than the American Heart Association diet. And are able to show the patients that, no, this very low fat diet with very high carbohydrates is causing this disorder, and that by shifting to a better diet we can improve that.

So to answer your question, I think yes, we can do a better job. I think we have to educate the medical providers on using these tests more appropriately.

I don't think it's 100 percent for everybody. In my practice it is, but it can be done just by education of the providers.

DR. STEELE: Dr. Remaley.

DR. REMALEY: Yes, I have a question for any of the clinicians who use the test. Could you break down in terms of the risk category of the patients -- low risk, intermediate risk, high risk -- your approach in terms of how you use these subclass tests, and whether you advocate using them as a screening test or as an ancillary test.

MS. SCHILLING: Well, given that I do a preventive cardiology clinic, the patients that I see 100 percent get this test.

If I were to be advocating to a primary care provider how it should do that, anybody with a strong family history of coronary disease, I would advocate an advanced lipid protein test looking for particle size, looking for LDL, looking for Lp(a), basically.

Anybody who has had an event with

normal cholesterol, if you will, I advocate using the test for that.

For routine screening I don't think it's the right test in a primary care setting unless you've got something else that you've looking at. If somebody has low HDL and high triglycerides and we call it the big gut no butt syndrome, but you know, you know they have metabolic syndrome, and that diet therapy should do.

The high risk patient is anybody to me that has had an event, or has diabetes, because they will have an event. One day a week I actually seen renal failure patients who are being listed for transplant. And that population is just as high a risk, so I also treat them to the higher standards with an LDL of less than 70.

Yes. I'm sorry.

DR. STEELE: Just finish up.

MS. SCHILLING: So then the

intermediate risk is anybody that doesn't fall into those two categories, which is a majority of the population that has multiple risk factors but no CAD, diabetes or chronic kidney disease.

DR. STEELE: Dr. Winter?

DR. WINTER: I'd really like to ask Dr. Cromwell or maybe one of the other speakers to respond to the last question. But in addition one of the charges of the panel is to look at the HDL subclasses, and I'd like some feedback from clinicians as to whether they've used HDL subfractions in their evaluations, and have they found it of clinical value.

MS. SCHILLING: Personally yes, I think it's of huge value. The way I explain to my patients is that your HDL are garbage men, and if you don't have enough active garbage men, and that would be your HDL-2, then you are not getting rid of garbage.

DR. CROMWELL: With respect to HDL

subclasses, the data were very confounding and confusing.

When we look on trial, on trial increases in HDL, small or large, are associated with improvements in outcomes.

If we look at epidemiologic data, you will find that there is a broad array of findings which include most consistently decreased amounts of large HDL associated with risk; increased amounts of large HDL not as associated with risk. So there is less risk with more large HDL.

But at the same time you can find individuals whose small HDL is not as problematic in certain populations as it is in others. So this is a mixed epidemiologic dataset.

In the book chapter that I supplied to the panel for its consideration, there is a diagram in that book panel from Framingham. And what we did was, look at numbers of HDL particles in total, numbers

of small particles, numbers of large particles, as a function of HDL cholesterol.

And you find some very interesting dynamics. As HDL cholesterol goes up, particle number goes up; but it doesn't go up symmetrically. Between 20 and 40 HDL cholesterol there is a big rise in numbers of small particles; and from 40 up numbers of small particles go down.

Numbers of large particles increase slightly from 20 to 40, but from 40 on large particles dominate. And because of those relationships, I think the answer to the question fo the value of subclasses in epidemiological studies will be variable depending on the characteristics of the population that you are looking at.

Those patients who are in a range of HDL cholesterol which have a dominant increase in the number of large particles will have a different association with that than individuals that are a different range

of HDL cholesterol.

So I think it is an open question with a lot of confounding data. More HDL is better, and I cannot say of data that suggests that only one type of HDL subclass would be beneficial to raise.

DR. STEELE: Dr. Tsia?

DR. TSIA: I was actually just going to make a comment on what Ms. Schilling has said. On one hand that you have -- you said that you work in a preventive cardiology setting. Therefore, that it's not the same as a primary care setting.

On the other hand you said that -- I was wondering since you work in a specialized setting, wouldn't you have discovered, or shouldn't you have discovered, metabolic syndrome with or without Atherotech?

MS. SCHILLING: You would think, yes, that it would have been discovered.

But I get patients referred to me with this questionable metabolic syndrome.

DR. TSIA: But since you were in a preventive cardiology clinic, you would probably have specifically measured for, looked for, metabolic syndrome?

MS. SCHILLING: Yes, I look for metabolic syndrome.

DR. TSIA: Even if Atherotech technology is not available to you, right?

MS. SCHILLING: Right, but I use the test then to measure success of treatment.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: It seems to me that a little bit of what you are talking about here is related to the art of medicine, which I don't think anybody wants to take away from physicians and clinicians.

But as far as I know, there are probably only two ways to make a determination as to whether something is

really clinically useful. One is, if in a study you have a very, very high predictive value. That is usually not the case, which you can obtain from a ROC curve and so on.

So the only other way then is if a prospective study is done, and it can be shown that some kind of a treatment or something of that sort shows clinical benefit and economical -- and is reasonable economically.

But from what you said, I don't think that the way you are approaching this has met either of these criteria, which would be for general use, let's say.

MS. SCHILLING: True. But the way that I look at it, though, is if you're looking at the prospective trial, and you look at the Quebec cardiovascular trial prospective study that showed that men with small dense cells yield higher numbers greater than 130 measured by Apo B had a 6.2 fold increased risk of developing coronary

disease.

Now there was no study done after that showing that lowering that or changing that made a difference. Intuitively it would make sense that if they were not in that category, there was this reduced.

So that's how I use those numbers. Again, it's not been proven, and to my knowledge there hasn't been any study that shows that changing the numbers makes a difference.

But I know that we're not getting anywhere by just treating LDL.

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: I was just going to also just make a point that when you look at more epidemiological studies of looking for small dense LDL, yes the clinical trials generally support it, and most of them, however you do have to be caution that if you go to areas like Finland, where the incidence of coronary artery disease is very

high, they tend to have very low levels of small dense LDL, in contrast to a country like Costa Rica, where it's nonexistent.

However, they tend to have very high small dense LDL, so it's quite possible you are going to overtreat a number of patients if you depend just on that, and miss a considerable amount of the other one.

So a lot of the traditional risk factors may be very helpful. I think you have to figure out are there going to be ethnic population, and determine that, and use that precaution.

MS. SCHILLING: I concur with that. We know that in especially in the sub-Saharan Africans that Lp(a) is not indicative of risk. So we just -- I just kind of push that aside.

But I started asking the African-American population do you have any Caucasian ancestry or any Asian ancestry. And nobody has been asking that, because

that would be an increased risk.

I don't know how to explain the difference in the population differences. Looking at epidemiology only I don't think is enough, because we have to look at the population with which we are faced as well and treat that individual. That's how I look at it.

DR. STEELE: Any other questions for any of the speakers?

No, well, the open public hearing session is now concluded.

I was reminded, there was a gentleman in the audience that wanted to make a comment earlier. We did offer it, but go ahead right now.

MR. SUPERKO: I'm Robert Superko from the Fuqua Arts Center in Atlanta, Georgia. I was 10 years at Stanford University as director of the lipid research clinic, 10 years at the University of California at Berkeley with Ron Krauss, did

a lot of the original subclass work, and now I'm in Atlanta working with Fuqua and Parvin and the CDC and stuff.

The quick point I'd like to make is that one question was, what is the clinical utility of the HDL subclasses. And there have been quite a number of studies -- Miller's in Great Britain, Johanson's in the Netherlands, the Framingham study that we initially did that was published in 1961. So the data is there from reputable investigators.

It's only useful however if it makes a change in what you are going to do to the patient. And the classic example is nicotinic acid. If you are going to decide to place a patient on niacin, if their triglycerides are high or HDLs are low, fine, you made the decision.

If you use niacin in somebody with an HDL of 45, that's where these tests come in, if you've predetermined how it's

going to change what you are going to do for the patient.

The justification for that comes from HATS, FATS or study at Stanford, SCRIP, which all these studies show that changes in the distribution of HDL, and even LDL, predict arteriographic change, but they are not independent of other measurements.

So if you tease out the triglycerides and the HDL you end up with a small group of about 20 percent in which you would not have predicted that based on the standard lipid test, but did do benefit.

Numbers need to treat illustrate this. The numbers needed to treat in statin studies are about 40 to 50. You have to treat about 40 to 50 people to get one prevention of an event. And in Greg's FATS study the number needed to treat was 10. In the HATS study the number needed to treat was three. Three.

So for scientist/clinician this

is sort of a no-brainer, which gets to Cindy's comment that why don't we just give everybody Niacin and a statin.

The final comment I'd like to make is that we had a meeting sort of like this with the CDC six months ago with a group of scientists and well known investigators in this field.

And I would respectfully submit to this committee that you might want to convene a similar group of people. And I would recommend Ron Krauss; I'd recommend Melissa Austin; and I'd recommend John Brunze; I'd recommend Alan Schneiderman, Preeter Quidovitch, Paul Williams who is the preeminent statistician in this field at U.C. Berkeley.

I've been PI and coauthor on a number of these studies. I'd be happy to participate. My fear is that you haven't heard the real scientific story here.

What you are have heard is the

bias from the industry that makes these machines, and that's reasonable from their standpoint. It's like hearing from a bunch of pharmaceutical people giving you their viewpoint.

So I'd suggest you might want to hear from the specialists, the people in the field that have done these studies who can answer all the questions that have come up, and people have said, oh, I don't know the answer to that, the answers are there.

So before you make a final decision, I respectfully submit you consider that kind of committee.

Thank you very much.

DR. STEELE: Thank you.

Are there any questions?

Dr. Winter.

DR. WINTER: I'd certainly like you to then flesh out what we're missing, what scientific data do we need that we don't have that these experts would share

with us?

DR. SUPERKO: Right. Well, what you have to flesh out is in what subsets and in what subgroups this information is clinically useful.

So for example, if you had Greg Brown here or John Brenzel they'd talk about the HATS study and the usefulness of measuring Apo A-1 which is similar to the HDL-2 region in predicting events.

In a multivariant statistical analysis in HATS, if you grade all the variables, and you ask what is the one variable that is the most predictive of arteriographic change, it's LPA-1. So it's the HDL subfraction that is most reflective of HDL-2s in this test.

In what group of people in HATS was that useful? Because HATS was a low HDL arteriographic study. And that kind of information you can glean, and therefore the decision might be, yes, these tests are

useful, but useful in this subset of people.

Another example is the National Asian Indian Heart Disease Study, which is a study we conducted and studied on Asian Indian individuals, because they have a very high risk of heart disease, about threefold greater than Caucasians. And the thing that popped out as extraordinarily predictive is low HDL-2, even in an Asian Indian man with normal HDL cholesterol.

So therefore, one conclusion might be, gee, this is a useful test in Asian Indian met with HDLs between 40 and let's say 50 or 55 in which you are trying to decide, should I give this person a medication.

It's useful in determining risk prediction in conjunction with other risk factors. So Quebec was mentioned, and in the Quebec study three risk factors were profoundly predictive. In a healthy population, if you have small LDL, and

that's the only thing you have, the relative risk increases threefold.

If you have small LDL and elevated Apo B, which is the preeminent marker of LDL particle number -- so B-100 is particle number -- if you have those two things your relative risk increases sixfold. If you have small LDL plus elevated Apo B plus elevated insulin, your relative risk increases twentyfold.

So I submit you could then say, well, there's a subpopulation in which these tests are going to help me identify people that I might want to do something different to.

There have been tons -- I've reviewed 500 papers for Medicare when Medicare agreed to pay for these tests in 1999, I went over 500 publications, all of which were NIH studies. Many of those were diet studies, exercise studies, some drug studies, all funded by the NIH. So there is

a plethora of data out there. That was 1999.

I think it would be very useful for the panel, if your decision is going to be, these tests are useful or they are not useful, to look at that kind of rigor, to go really deep and understand what is known and not known which is more important.

DR. WINTER: The first studies that you mentioned, then, do they favor measuring Apo A-1, the Apo lipoprotein? Or fractionated it to an HDL-3. Because there is a strong correlation between Apo A-1 and total HDL.

DR. SUPERKO: Well, what I'm talking about is Lp(a)-1, so this is a method that Fouchard (phonetic) developed in France. And it's not the plasma A-1. So it's the lipoprotein particle that has A-1 only on it. So you can have A-1 only particles, and then particles that have A-1 and A-2.

So the Lp(a)-1 only sometimes is confused when you say it's a one. But it's different than measuring just Apoprotein A-1. That's a very good method for determining risk in some studies, and it's been used in Fouchard's work preeminently.

DR. WINTER: What is the method for that?

DR. SUPERKO: Affinity chromatography, thank you very much.

So anyway that kind of information can be very useful to you, and whether or not this committee will pronounce lipoprotein subfractions useful or not useful, I'm concerned that you can't make that decision today, unless you have read the literature in depth.

Anyone else want to hear my opinion?

DR. STEELE: Dr. Zhang.

DR. MARCOVINA: In the Greg Brown study, sir, Apo-1 with Apo-2 particles was

determined by Fouchard method. It is a method that is being developed at the University of Washington by Dr. Change, and the subsequently Fouchard developed it and commercialized a derivation of the matrix. It is not the matrix that was used by Greg Brown.

DR. SUPERKO: Thank you for that correction.

DR. STEELE: Dr. Zhang?

DR. ZHANG: Could you summarize what are really missing in the FDA presentation in your opinion? Exactly what kind of literature we are missing, or we haven't go the so-called full picture. Exactly made your points, especially as it relates to subclass. You have to point out exactly -- we had extensive discussion about LDL, HDL, what exactly is missing.

And also for finding solid data, without peer review published.

DR. SUPERKO: Well, one thing in

your field that Parvin addressed I think very, very well is laboratory methodology. So the field as I think you've appreciated is very different in terms fo methodologies used in different studies, and it's never been standardized. So I totally agree with this point about the difficult of standardization, and either tweaking methods to come to a standard, or using a standard for each one of those.

But what is critically important for this panel to appreciate is, none of these studies, none of these methods, have been standardized to any known standard. The only standard we ever used was the analytical tricentrifuge at Donner for many years. That was sort of the gold standard. That machine now has falled apart. We can't use it. It's too old. There are no parts for it.

So unless you have some kind of standard, then how do you know what you are

measuring is accurate.

DR. ZHANG: I'm sorry, this is standardization. We have an extensive, intensive discussion today. I want to hear something really new, new subclasses you mention, you could point out, or new idea beyond what we have discussed. Because you made a very clear statement, say we're missing something.

I want to know exactly -- don't have to go to standardization. We know this. We already know this problem now. Tell me exactly what we are missing today.

DR. SUPERKO: One thing you are missing is the history of lipoprotein subfractionation and its relation to coronary disease. So for example are you aware of John Goffman's 1951 paper in Science, the 1961 paper in circulation about the ANUC data in the Framingham study? Very important, a class paper that everybody has to read.

There are a series of papers, and I've move up from that, in terms of predicting events, particularly in terms of the relationship of triglycerides and HDL to helping tease out who needs and doesn't need this. So the work by Melissa Austin is very seminal in this. A lot of the work that we did at Berkeley is very useful.

You can use triglycerides-HDL ratios. You can use an LDL Apo B ratio. You can do tests that are fairly easy to get today to tease out people that you don't need to do subclass testing in. So that would be one very important point is, is this testing useful for everybody, or should you select subsets based on easily accessible laboratory tests, point number one.

Point number two, what's the evidence that if you have this information and you act on it, it's going to be of any benefit to your patient? And there are two

ways it's beneficial: one is that it changes the laboratory test. Your numbers get better; things change. Not outcomes, but laboratory things. So there is a whole series of diet studies, exercise studies, drug studies, studies with statins that have shown absolutely no change, studies with niacin, studies with fibrates.

So if you are going to recommend this is useful, then you also have to embrace the idea that it's useful for what. And so appreciating the plethora of data on diet studies, exercise studies and drug studies is useful.

Third is appreciating the effect on outcomes, so there is no primary outcome study. That doesn't exist. What we've been relying on are arteriographic studies, because we cannot get a primary outcome study funded through the NIH. It's too big, too expensive. They have turned down the applications many many times. So all you

can do is fall back on arteriographic studies.

When you look at those, you need to appreciate the interaction of once again triglycerides, HDL, LDL-Apo B ratios on teasing out the people that you could use this test in usefully and people that you don't have to do the test because your standard measurements identify them already.

So if you appreciate that today, then fine, you don't need the experts. My suggestion is that more information is useful.

DR. STEELE: Dr. Tsia.

DR. TSIA: Dr. Superko, I respectfully submit the fact that you may not have read all the literature of the panel members here, and therefore you are saying we have not read or done part of the work in this area, and I respectfully disagree with you.

We have Dr. Marcovino, we have

Dr. Remaley, myself. I have begun doing small dense LDL in the `90s with Dr. Hunninghake. So I think we have read a few papers. So you are assuming a little bit.

DR. SUPERKO: Well, I apologize if I insulted anybody, but I was referring mainly to the information that you've received during this day's session.

DR. STEELE: Dr. Levinson?

DR. LEVINSON: Yes. You mentioned -- and you could comment on this, and I enjoyed your discussion -- you mentioned, though, that an odds ratio, I guess it is, or maybe it was a risk ratio --

DR. SUPERKO: That was a risk.

DR. LEVINSON: -- if I'm all together, went from 1:5, to 1:6, and finally up to 1:20. But actually -- and you also mentioned, though, the difficulty you do in perspective studies, I appreciate that, in outcome studies like we talked about before. But in any case, it could be estimated that

an odds ratio of 1:200 would give a true positive frequency of about 56 percent and a false positive frequency of about 5 percent, and, you know, that's not very good for prediction, 56 percent, and that's an odds ratio of 1:200.

So when -- and although we see these odds ratio all the time in the various journals of 1:1.3, indeed unless you're doing an outcome study in order to talk about an odds ratio of 1:20, you're not really predicting -- you're not really discriminating anything very well. You really have to probably get up to at least 200 to get a 56 percent to a positive frequency, and yet above that to get very good discrimination.

Could you comment on that?

DR. SUPERKO: So I think the issue you're bringing up is that relative risk increase doesn't necessarily correlate with discrimination in terms of prediction

of individuals. I think that's very valid. The clinical issue is if you have somebody who is either at high risk or with disease, how will you treat them, and do laboratory tests actually give you insight into that?

So if we go back to that same example, with Small Alio Apo B high insulins, if that's an individual with coronary disease, you need to treat something. And we focused so on LDL, if the patient has high insulin, then as a clinician scientist, I might switch to focusing on treating that insulin, even though there's not a long-term outcome study because that's the science, as you mentioned, of medicine.

I share your concern that people focus too much, and rely too much, on the predictability and accuracy of laboratory tests when, in fact, the field is changing towards treating the disease and not treating a laboratory number. And I think

that's where your issue is coming from as we can only use laboratory numbers to calculate predictability, when actually what we need to do is have some measure of disease and disease chance, which non-invasically, of course, is occurring and all these tests are being involved in. Does that sort of address it or was I talking around your question?

DR. LEVINSON: Thank you.

DR. SUPERKO: And I didn't mean to insult anybody. I know you guys have done a whole bunch of work, and -- Yes. I'm sorry. I know you do, and I apologize.

DR. STEELE: That's fine. Okay. Thank you. Any further questions or comments? Yes, Dr. Watson.

DR. WATSON: Dr. Superko, I would just have to say one thing in relation to what you just said. If you were going to focus strictly on the insulin because that was the predominant risk factor, then you'd

be making a mistake because the clinical trials that we have currently, either using pioglitazone or rosiglitazone, the best insulin synthetizers we have, have shown an excess of cardiovascular events not a decrease in cardiovascular events.

So this is the problem with using that kind of data. We have to be careful that we're not leading people down the wrong path.

DR. SUPERKO: True. But you also know about the studies that have used weight loss in terms of diabetes prevention and of that form in diet study and the troglitazone study. So there are studies that show dramatic reductions in the development of Type-2 Diabetes, and the assumption is that has to do with treating insulin resistance.

DR. WATSON: The most recent study in rosiglitazone also showed an improvement in the progression to Type-2 Diabetes, but the cardiovascular events were

statistically significantly increased.

DR. SUPERKO: Right. Well the therapy that one would use the most would be diet, exercise, and weight loss.

DR. STEELE: Dr. Zhang?

DR. ZHANG: I would like to make a -- just a follow-up to the comments. I respectfully disagree your just stated a few minutes ago in this panel should not make any decision because we are missing a list of experts you named. I respectfully disagree because it's a public hearing, I really would like to make the statement here. This panel does have a lot of expertise in a variety of fields, including the research plus general lab evaluation, epidemiology, toxicology, and regulatory issues.

So I don't believe for such devices and all these painful exams should focus a balance of experts. I respectfully disagree because we lack a set of experts

you like or yourself are part of, you draw a conclusion, say this panel should not make any decision or recommendation. That's it.

DR. STEELE: Thank you, Dr. Zhang.

DR. SUPERKO: Am I off the hot seat?

DR. STEELE: Yes. Seeing no more questions, the open public hearing session is now concluded. At this time, we're gonna go through the FDA questions are going to be handled. We're gonna do that before the break. We're gonna try to get a couple of them out of the way before the break.

Before you start, it is my understanding we're gonna be polling the panel on the first two questions -- there are several parts to the first two questions. I guess by convention, we'll be rotating around the table. The -- apparently the consumer representative is the second to the last, so we'll go by that

person, and then the industry representative is the last person on the panel to comment.

PANEL RESPONSE TO FDA QUESTIONS

DR. WOOD: Based upon the current state of knowledge, please provide input on the following questions:

Question 1. Is there sufficient information available to conclude that HDL and/or LDL subfractions can be used to assess the patient's risk of developing cardiovascular disease?

DR. STEELE: Okay. We're going to start that with Dr. Remaley, and we will go around the table this way.

DR. REMALEY: I think the preponderance of the evidence does show that they are useful, although I am concerned in terms of making a global assessment in terms of their utility, and I was actually hoping to get some feedback in whether they're useful in terms of screening versus as an ancillary test.

I think, at this point, I would feel comfortable with using them as an ancillary test in those patients that have an intermediate risk, and not to decrease the score, but to increase the potential risk factor to do more aggressive therapy. In that case, I think it has a limited downside in terms of under treating patients.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: Well -- thank you. Well these questions are sort of general. And so to assess a patient's risk of developing coronary vascular disease, I would say, to some extent, yes. I don't know though that outcome studies have really proven they're better than something else. To diagnose dyslipidemia, again --

DR. STEELE: No. Those questions will be separate and will be polled on each sub-point. Just 1a we're talking on right at the moment.