DR. LEVINSON: Okay. We're only talking about 1a. Okay. So that would be to -- that's to -- I guess I'm on -- am I on the wrong page? Oh. I'm sorry. I'm on the wrong page. That seems to be the problem.

To assess a patients risk -- oh yes -- of developing coronary vascular disease. So we're only asking about the first one. And I would say, to some extent, yes. That is all I can say.

DR. STEELE: Dr. Watson.

DR. WATSON: I would say yes, there is some evidence in certain populations these test can be useful to help clarifying risk, never to be used instead of standard risk algorithms, but to help, perhaps, supplement them.

DR. STEELE: Dr. Winter.

DR. WINTER: I think there's controversy about the HDL subfractions or LDL subfractions. There does seem to be a relationship between various fractions and

cardiovascular risk. My prejudice would be that these not be first line studies, and that they predominately be used in people that do not have traditionally recognized risk factors.

DR. STEELE: Dr. Grines.

DR. GRINES: I think I agree with everything Dr. Winter said. It seems that the preponderance of evidence is in people who are close to already meeting the goals or with normal lipid profiles already. But if a patient has high LDL just -- or high total cholesterol, low HDL high triglycerides, that it probably -- I don't see that it adds anything to those type of patients.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: Yes. I think so in certain populations, as was stated before, and especially for the lipid particle number. It seems a little less clear with the HDL subparticles.

DR. STEELE: Dr. Zhang.

DR. ZHANG: I believe there is hope to do such a subclass analysis. And in terms of the question asked, is there sufficient data, sufficient information? My answer is no. We do not have sufficient information. But there is hope to continue such study or development such as this.

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: I believe that the LDL subclasses have been established to assess the risk of developing cardiovascular disease. I think there's biological basis for a smaller denser particle in, perhaps, increased number. I believe the epidemia logic and clinical trials confirm that the small dense particles are atherogenic.

However, it's unclear whether this added information, as far as clinical practice, is any more beneficial for traditional assessment. And based on a number of things, the unreliability

standardization and variation in defining what they are.

DR. STEELE: Dr. Marcovina.

DR. MARCOVINA: Yes. The current status of knowledge is by far stronger for LDL, particularly for LDL particle number, then used for HDL. But, yes, I would suggest the use in the selective cases.

DR. SHAMBUREK: Sure. For HDL, I believe that the information is too controversial to use it at this time.

DR. TSAI: I basically agree with everybody's -- what everybody said, that there's a large amount of information showing that small dense LDL, whether the size of the particle number, etc., that assessing subfractions of some clinical use, but should be limited to certain populations, the high-risk populations.

DR. STEELE: Okay. I guess, in summary, I think in general the panel feels that there is some useful information in

assessing a risk -- a patient risk for developing CVD with especially the LDL subclasses, the small dense LDL particles. I think the committee or panel was less -- less enthused about LDL subparticles. HDL -- excuse me. I'm sorry. What did I say? HDL.

I think that the concerns that were brought up were that global use was probably not at this time appropriate for the subclasses, and that these tests should be utilized only in certain specific populations.

Any other comments that I've -- I'm sorry. I forgot to include the consumer representative. Dr. Loew, I'm sorry.

DR. LOEW: Thank you. I would agree with the comments already made. And the one aspect that I think was mentioned before is that it would be nice to have -- of course, it's an expensive prospect -- but to have a clinical trial that really could

find some specific solid answers to this.

DR. STEELE: Thank you. Thank you. And Dr. Worthy.

DR. WORTHY: I concur with the input of all of the other members of the panel, certainly in -- as respect to LDL subfractions. I think HDL, I would agree, is more controversial. One of the things that I'd like to see is studies that would define which of the subfractions are, in fact, clinically important.

I used to, when I was in Rutgers laboratory, I used to talk with physicians all the time, and interpret lab results for them. And to have the potential for seven or ten different subfractions and try to interpret a large number of results becomes very complicated and very difficult, especially for the doctor who has to now make the decision.

So if studies can be done to identify which are the most critical, which

are the most atherogenic, which ones of the, for example, LDL subfractions are the most germane for clinical ethicacy, that would be a big benefit for, I think, for everybody concerned.

DR. STEELE: Thank you. And I would amend my comment to concur that we do need better information in which specifics subfractions need to be analyzed, and that that goes in part with the fact that we do not have enough information at this time to make those decisions.

DR. LEVINSON: Can I just make a comment about that? It's just that, regarding what you just said, a big question, it seems to me, is -- a big question, it seems to me, is whether or not the study so far shows such great promise of these methods that it would be worth going ahead with a very, very expensive progress -- perspective study in order to prove this. And my conclusion, at this point, would be

no. Do you see what I mean?

DR. STEELE: Well I think that's beyond the scope of us at this particular point. Next question.

DR. WOOD: All in the same lines, is there sufficient information available to conclude that HDL and/or LDL subfractions can be used to diagnose dyslipidemia?

DR. STEELE: Okay. And I'm going to start this time with Dr. Shamburek, and we'll go across the front of the panel here.

DR. SHAMBUREK: Yes. I believe LDL subfractions can provide additional information in a patient that has these LDL, when LDL alone may underestimate the risk. However, I think it's unclear whether it provides clinical information above what you would get if you measured HDL triglyceride and non-HDL. And I would also add, although it's not traditional, Apo B adds a lot of information about particle size that could also be used currently.

As far as HDL, I don't believe currently we have enough information to know that it's beneficial in the diagnosis.

DR. MARCOVINA: I concur. More status are needed for HDL. For LDL, we needed to define whether or not it's more clinically relevant to measure LDL particle size or to measure LDL density. But I would definitely say that can be used for diagnosis of dyslipidemia.

DR. STEELE: Dr. Tsai.

DR. TSAI: Yes. I agree that this does provide some additional information. On the other hand, as you have heard throughout, it also, in many cases, provides confusion for clinicians. So a lot more work needs to be done, not just standardization, but also -- yes, standardization, in many ways, in more ways than one, so that we can help our clinicians to understand the true interpretation of the use of this test.

DR. STEELE: Dr. Remaley.

DR. REMALEY: Yes. I think, as an ancillary test at this time, I would feel comfortable using the, particularly the LDL subfractionation method for just to diagnosis dyslipidemia.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I would say it could be used to diagnose dyslipidemia, but I would I also say, as far as the subclass B is concerned, in my view, the evidence indicates it is not an independent risk factor as compared to HDL cholesterol and total cholesterol. That's what I think.

DR. STEELE: Dr. Watson.

DR. WATSON: I would say that the LDL subclasses can, yes, be used to diagnose dyslipidemia. But HDL, I think it's absolutely not there yet.

DR. STEELE: Dr. Winter.

DR. WINTER: When I look at the term, diagnose dyslipidemia, I think, to me,

that's more than just characterizing an abnormality. It's saying is there a specific hyper dense LDL disease that's independent of other risk factors. And I don't think there is. I think the data predominately shows that dense LDL is associated with a metabolic syndrome. And for that reason, I don't support it being used as a diagnostic term for the diagnosis of disease, nor do I support HDL.

DR. STEELE: Dr. Grines.

DR. GRINES: I think that I could see it being used to "diagnose dyslipidemia." I don't know if we really know, with 100 percent certainty, what the traditional definition is since we're seeing all these people with relatively normal lipids that are having cardiovascular disease. And if this allows us to scrutinize that more and be more accurate, then yes, I think it will help diagnose and redefine dyslipidemia.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: I may be kind of like Bill Winter. I have a little hangup on the question itself. The term dyslipidemia, to me, says a laboratory abnormality. So can this laboratory test be used to define a laboratory abnormality? That is, in of itself, its definition, right? So can this -- can abnormal values of say particle number -- are those -- can those be used to diagnose or be associated with an increased for something? That's kind of what was in Question A.

I feel, yes, there's evidence for particle number in association with cardiovascular events, but to diagnose -- so is the question -- is abnormalities compared to a so-called normal population, is that in itself a disease? I don't know. I don't know that there's evidence for that. So I kind of have a hard time with the question itself. So that's what I think.

DR. STEELE: Okay. Dr. Zhang.

DR. ZHANG: I think in this certain population, patient population, this LDL subclass can be useful to help to diagnose such a, whether or not I should call it disease. Probably not as just my neighbor just mentioned. For HDL, my opinion is certainly, at this moment, certainly no. No. And to make sure answer to the question is yes, a lot of work should be done, especially in clinical study. You have to demonstrate, say this abnormality of LDL or HDL really relate to these we define. Thank you.

DR. STEELE: Dr. Loew.

DR. LOEW: Well certainly, as far as HDL is concerned, I think it's not useful based on the data that we've seen. As far as LDL goes, there seems to be more evidence, but I am concerned about the same things that Dr. Gronowski is, namely that this seems to be a circular question. If

dyslipidemia is a laboratory measurement as opposed to a clinical condition, which I imagine is what Part A was dealing with, then it really does become circular. And so there's some question about the usefulness of the question itself.

DR. STEELE: Thank you. Dr. Worthy.

DR. WORTHY: I guess I read the question as more as an aid to the diagnosis of dyslipidemia as opposed to the diagnosis of dyslipidemia. And in that case, I think it's -- it does play a role, certainly the measurement of LDL subfractions.

And I think one thing that hasn't really been brought up today is that LDL cholesterol measurements can underestimate the amount of LDL because it is only measuring the cholesterol associated with the lipoprotein as opposed to the mass of LDL that is present. So there is potentially the added benefit of being able

to use LDL subfractions to make sure that in fact you -- that you have not underestimated the amount of LDL present.

DR. STEELE: Okay. Summarizing the thoughts of the panel, LDL subfractions can be useful in the diagnosis of dyslipidemia. The general feeling -- the general feeling was that this -- that HDL subfractions were not going to be useful, at this time, in the diagnosis of dyslipidemia.

There was concern expressed about this information -- providing -- this information might cause confusion to the clinician. And there was a large portion of the panel that felt that the subfractions did not meet the criteria of the word "diagnosis," and had trouble with that particular word.

DR. WOOD: Is there sufficient information available to conclude that HDL and/or LDL subfractions can be used to

monitor treatment of dyslipidemic patients?

DR. STEELE: I'm going to start the question -- the answering with Dr. Watson, and we'll move down that way.

DR. WATSON: I don't think there is good enough evidence to say that you can use it to monitor therapy because I think for that you would a need clinical intervention study showing that changing the parameter via intervention improves outcomes, and I don't think we have that yet.

DR. STEELE: Dr. Winter.

DR. WINTER: No. The answer to the question is no. There's no data to support that other than reflection of clinicians. No randomized control trial.

DR. STEELE: Okay. Dr. Grines.

DR. GRINES: No. I haven't seen any of that data presented today.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: I agree. I also

feel there's not enough evidence for that.

DR. STEELE: Dr. Zhang.

DR. ZHANG: There is no supporting data for such a ...

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: I believe that the lipid metabolism is dynamic, and LDL has been helpful in understanding the transformation of the particles, such as particle B to particle A that occurs with treatment. However, improvement also occurs in HDL triglyceride non-HDL, and I think you could throw in Apo B. So I don't see that it adds additional information to the clinician.

However, I do want to point it's been an extremely important advancement in understanding clinical trials and in understanding the pathogenesis of many disorders. As far as HDL, I think we still need information.

DR. STEELE: Dr. Marcovina.

DR. MARCOVINA: I say no for HDL. For LDL, we can reach LDL treatment goals and reach Apo B treatment goals, and that the same can then be applied to LDL particles. But to monitor the therapy, I would say no.

DR. STEELE: Dr. Tsai.

DR. TSAI: No.

DR. STEELE: Dr. Remaley.

DR. REMALEY: Well I was persuaded that there may be some useful information for LDL particle size. I don't think we have enough information to -- and that's not a rule here to have -- design new treatment goals, but I think there is hope that the LDL particle, and perhaps some of these other subfractions in the future, may be useful. But at this time, no. And, again, I don't think that's a role here anyway.

DR. STEELE: Thank you. Dr. Levinson.

DR. LEVINSON: I agree with the other panel member -- most of the panel members that it would not be useful for monitoring treatment goals. I would say that the National Cholesterol Education Program of the primary LDL and the secondary non-HDL cholesterol depending on dyslipidemia's would be the way to go.

DR. STEELE: Dr. Loew.

DR. LOEW: No.

DR. STEELE: And Dr. Worthy.

DR. WORTHY: No.

DR. STEELE: No. I think there is almost a universal agreement that, at this time, for LDL and HDL subfractions, there is not enough evidence to use this in the monitoring of treatment of dyslipidemic patients.

DR. WOOD: Finally, for Question 1, is there any other use for the HDL and/or LDL subfractions that have not been brought up at this time?

DR. STEELE: I'm going to start with Dr. Shamburek again. He had comments on that before.

DR. SHAMBUREK: I don't think -- no, not at this time for either one.

DR. MARCOVINA: No.

DR. TSAI: More research.

DR. LEVINSON: I would say there's limited research, but there is, again, some information that is choosing niacin or statin may be -- may want to interpret the microprotein subfractions. It may provide for information. But at this point, I don't think the evidence is strong enough to say that it is useful.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I would say, regarding that, that the evidence indicates that lowering LDL lowers all of these, and though there may be some variation or changes in some of the subtypes versus others, that there is no evidence for any

other use.

DR. STEELE: Dr. Watson.

DR. WATSON: No evidence.

DR. STEELE: Dr. Winter.

DR. WINTER: No.

DR. STEELE: Dr. Grines.

DR. GRINES: No.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: No.

DR. STEELE: Dr. Zhang.

DR. ZHANG: No.

DR. STEELE: Dr. Loew.

DR. LOEW: No.

DR. STEELE: Dr. Worthy.

DR. WORTHY: I think there's some value in research modes to either look at better understanding of modulations in the cascade or in terms of understanding the mechanism of the new drugs under development.

DR. STEELE: Okay. Summarizing for HDL and/or LDL subfractions for any

other use, the committee in general said no, except for a couple of comments about research -- continuing research in this area and for using this as research applications to look at various aspects of metabolism pathology and such. Next.

DR. WOOD: Question 2. Is there sufficient information -- if sufficient information is available for clinical use, should HDL and/or LDL subfractions be used as a stand-alone test or alternatively as an adjunct test to be used with other traditional risk assessment tools, such as total HDL and LDL cholesterol, as well as clinical judgment?

DR. STEELE: Okay. And this time we'll take both those questions at the same time, and we'll start with Dr. Zhang.

DR. ZHANG: To the first question, I would say no. And to the second, I would say yes.

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: As far as LDL for stand-alone or as adjunctive, I don't believe there's enough data. I think we've mentioned that there are problems with it as far as HDL. I think we still have to wait for a lot more information.

DR. MARCOVINA: No as a stand-alone test. Yes with the classic lipid profile, but in selected cases.

DR. STEELE: Dr. Tsai.

DR. TSAI: No as a stand-alone test, absolutely not. Yes as an adjunctive test.

DR. STEELE: Dr. Remaley.

DR. REMALEY: I agree. No and yes.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: Actually I would say no and no because I don't really see how it can be used as an adjunct test, except in very selective cases. Maybe in very selective cases it could be used.

DR. STEELE: Dr. Watson.

DR. WATSON: No as a stand-alone. Never. And as an adjunctive test in selected populations.

DR. STEELE: Dr. Winter.

DR. WINTER: No as a stand-alone test. As an adjunct -- only -- and then to be used only in individuals that have normal lipid profiles, yet are felt to be at risk for cardiovascular disease for some other factor, for example, family history, development of angina or MI.

Since we've already seen that LDL doesn't recognize half of the people that have heart disease, I think we have to be very selective of who this test should be run in that have normal LDL's because that would define half the population. And I think that, as I've said earlier, not everybody that gets heart disease has abnormal lipids, and I think there's been a predominant thought that we have to find a

lipid abnormality in everybody that has cardiovascular disease. I don't think that's the case.

And I'd also just say one comment, when we use angiography as an outcome measure, we have to be careful as well because some of the people that have the most severe lesions have collateral circulation, and those lesions aren't the lesions that undergo thrombosis. At least half the people that have MI's have 50 percent stenosis, not a 90 percent stenosis.

DR. STEELE: Dr. Grines.

DR. GRINES: I'll say no to the stand-alone, and yes for the adjunctive. I still -- you know, I still feel that even though -- we have other risk factors to explain. Some of the vascular disease, there's still cholesterol that's being deposited in the coronaries, even with you know, underlying patients with family history in hypertension. I think any type

of test that might help us predict who that's going to happen in would be potentially useful.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: No as a stand-alone test, and maybe in populations, certain sub-populations. But again I still feel that we need some outcome data, some prospective studies.

DR. STEELE: Dr. Loew.

DR. LOEW: Yes. No for the first one, and likely for the second one. But I also would be very much in favor of perspective trials.

DR. STEELE: And Dr. Worthy.

DR. WORTHY: No as a stand-alone. Yes as a adjunct. And I think we still need much more data to really know which sub-populations will really be most benefitted by the additional testing.

DR. STEELE: Excuse me. Dr. Watson.

Dr. WATSON: I'd like to amend my answer to say the select populations that it should be used in to also -- I agree with Dr. Winter. Never in someone who already has an abnormal lipid profile.

DR. STEELE: Okay. I think the unanimous opinion of the committee was that HDL and LDL subfractions should never be used as a stand-alone test. As an adjunct test to be used with other traditional risk assessment tools, there was a general opinion that it should be available, at least for the LDL. There was expressed concern about for HDL.

And there were several people who made the point that it should only be used in selected populations, especially those who -- never to be used in a population that already has an abnormal lipid profile.

Dr. Gutierrez?

DR. GUTIERREZ: Yes. Could -- can I -- can we have a little more discussion on this?

And the point that I would like you to flush out for us that would be very helpful is there are several people who have said that this would be useful in selected populations. So that being the case, what we would like to know is, what kind of -- if somebody is going to come in with a summation for this type of test in a selected population, what should we be -- what kind of selected population should we be looking at, and how does one look for accuracy and all those other issues based on just that population?

I mean do we require them to come in with data for everybody, or just a selected population, and what exactly are we looking at, and how do we deal with the limitations of the test that that would cause?

DR. STEELE: That's a multi-component question. We've asked -- maybe we could start with defining the selected populations first and maybe if someone could maybe bring in the terms of accuracy and I guess

precision and such. We will go starting with Dr. Winter, and we'll work back this way this time.

DR. WINTER: I think the selected populations I'd recommend are individuals that have let's say, normal lipid profiles, if they have other risk factors, obesity, hypertension, diabetes, I think the additional information that they have increased stents LDL could be informative. But I think to propose that all normal lipidemic patients should have a LDL fractionation at this point is not founded by the data -- not supported by the data.

DR. STEELE: Dr. Watson.

DR. WATSON: I would say only in individuals who have either a personal history or a family history of atherosclerosis out of proportion to traditional risk factors, and that can be lipids, blood pressure, anything.

DR. LEVINSON: The only selected population I really could think of -- I see two things regarding this. One is, unfortunately, a

person that's had an event and doesn't have known risk factors of any kind. That would be what I would consider a selected population. So the other would be a question, I suppose, just like it is now, the art of medicine. Some doctors are using these tests, they seem to think it's useful.

There are no outcome studies, I think, that proves that, but that's the art of medicine. So those would be the two kinds of cases I could imagine and I think the first is really much more valid.

DR. WINTER: If it's a personal opinion, the horse is out of the barn. I just don't think that's a valid indication. I think you have to be more prospective.

DR. STEELE: Dr. Remaley.

DR. REMALEY: I think I would feel comfortable only in the patients with intermediate risk where there's a dilemma in terms of how aggressively you should treat them, whether you should get down to the 1:30 or 1:60

target goal. If you recall, in that category, that's where the NCP recommends ancillary tests. And I think it should only be used as a positive risk factor.

I do feel uncomfortable if someone turns out that they, from the subfractionation test, has a pattern A, and therefore has decreased risk and not treat him as aggressively. I think the way to handle that is if it's only used as a positive risk factor so that you would -- because I think, overall, we under diagnose and under treat. And I think that minimalizes the downside using the test.

DR. STEELE: Dr. Tsai.

DR. TSAI: I agree with Dr. Remaley that it should be used in people with intermediate risk, and also with Dr. Watson about having family history.

DR. STEELE: Dr. Marcovina.

DR. MARCOVINA: Individual with intermediate risk to aid the physician to decide that the treatment, or how aggressive the

treatment should be.

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: I would just have to say that I was one who did not say to do it, but we have heard two categories, one of people with a personal history or a strong family history, and the other of intermediate. Well if you have a personal history, you're going to be treated aggressively anyway.

As far as the intermediate, I think based on existing data and studies, I don't think that we have the information on what to do. And then the next thing is, what to treat for and what guidelines are you going to follow.

DR. STEELE: Dr. Zhang.

DR. ZHANG: I think such a discussion pretty much in theory, and I would like to see some outcome data. If you really want to limit a specific test to be used in certain conditions, you have to have a strong outcome data of support.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: I think that there's not enough data to say which subpopulations. I think that more research is needed, and I guess I would start my research with the populations that were mentioned, so your populations that have high other risk factors, but perhaps a normal standard lipid profile, or people that don't respond to normal therapies. That would be a great population to begin those studies with.

DR. STEELE: Dr. Grines.

DR. GRINES: well I agree with what everybody else has said about the intermediate risk, strong family history, and then anybody with a cardiac event if they have a relatively normal lipid profile. We also are getting into the situation where we're doing a lot more scanning of patients with CT angiography and calcium scores.

And so I think this raises another issue about how to handle that if they have just mild coronary disease but no clinical symptoms,

or abnormal stress tests at this time. And so I think that would be another interesting area to look at.

DR. STEELE: Dr. Loew.

DR. LOEW: I'd rather reserve judgment until there were more clinical studies.

DR. STEELE: Dr. Worthy.

DR. WORTHY: I would concur with the panel.

DR. STEELE: Okay. Thank you. There were several I guess divisions in this -- on this particular question. I think the majority were concerned about, at this time, and some went from no use to wanting to have more data before they made an opinion at this particular time as to what selected population should be monitored with this test.

There was a sizable group of the panel that wanted or thought that the intermediate risk group was an appropriate group as a selected population, and then there was, of course, expressed the opinion that it should be

used in people who had normal lipid profiles with other risk factors, or a person who had family history or individual family -- individual or family history that was out of proportion to their lipid profile.

Dr. Remaley?

DR. REMALEY: If I can just quickly...

DR. STEELE: Sure.

DR. REMALEY: If I can just quick -- but most of those people you just spoke about would be intermediate risk by the NCP Guidelines.

DR. STEELE: Thank you. And that was brought up by Dr. Shamburek. Yes. Dr. Winter.

DR. WINTER: Can I also say that saying who it might be used in isn't necessarily an endorsement of its use. There's a distinction between the two. I mean I don't mean to say that I endorse it being used in that population, but if it were to be used in any

situation, that would be the group that I would use it in.

DR. LEVINSON: I agree.

DR. STEELE: Okay. Yes. Okay. Thank you. All right. We're coming up on to our 2:45 break, and we will have -- I think was it -- a 15 minute break. To the panel members, please do not discuss this on the outside. And if we'll get back on time, we'll get out on time. Thank you.

(Whereupon, the forgoing matter went off the record at 3:06 p.m. and back on the record at 3:25 p.m.)

DR. STEELE: Please can we take our seats? And we're coming down to the home stretch here. All right. We will continue with the FDA displaying the questions. And this will be handled a little differently. The panel will not be polled, but will be -- it'll be open to comment after the question is read.

DR. WOOD: When used either as a stand-alone test or in conjunction with other

lipid measurements, with values defined as non-cardiac risk by the NCEP ATP III Guidelines, will changes in treatment based upon the abnormal lipid subfractions pose an acceptable level of benefits compared to risk to the patient?

DR. STEELE: Okay. That question is open for discussion. Dr. Tsai.

DR. TSAI: I think the answer is a qualified yes. It depends on in whose hands this has been done that I think there are two levels of problems. One is that, as we discussed before, that these test results are fairly complicated so that it may or may not be useful for the primary partitionist. But for the right people it could be useful.

DR. STEELE: Any other comments? Dr. Watson.

DR. WATSON: I think the test would not pose a harm only if the results are used to talk someone into treatment rather than talking someone out of treating.

DR. STEELE: Excuse me. Can you repeat that again?

DR. WATSON: I probably didn't -- I don't know how to phrase it well. But I'm just saying, use it in order to maybe intensify treatment rather than withhold treatment.

DR. STEELE: Okay. Thank you. Dr. Remaley.

DR. REMALEY: Yes. I would agree. Just to repeat, I'm just saying if it's used as a positive risk factor in the parlance of where they normally describe these, then I think its fine, assuming that it's, of course, done correctly. And I think that minimizes its downside.

And, again, I think we have to keep in mind that, overall, we under diagnose and under treat cardiovascular disease, so that's why I feel this strongly that it would probably would be useful in that way.

DR. STEELE: Dr. Worthy.

DR. WORTHY: I had found a couple of

articles that kind of back into this question. And basically what I found was that, in these papers, they use the same doses to treat to reduce LDL cholesterol concentrations as they did in subsequent follow-up studies to look at changing LDL subfraction levels. So basically they were using the same dosages -- same drugs, same dosages, whether they were treating for LDL cholesterol or for the lipid subfractions.

DR. STEELE: Anybody else? Dr. Levinson.

DR. LEVINSON: I would say there is not enough evidence to indicate that it should be used for treatment.

DR. STEELE: Dr. Shamburek.

DR. SHAMBUREK: Yes. I would comment, again, the benefit would be there if we did know that we could identify those patients that we can't by the current classification. Now a risk potentially is if we this information and we treat patients with drugs that do have side effects, when we don't

have the data right now to do it.

So, yes, we all know and have numerous patients that don't qualify by the guidelines, but we don't know that for sure by using this test. There are very good studies that have picked out the populations in all that, but if we look at this as a whole class, maybe we should be looking at it as individual tests. But we're trying to clump all these.

If we just go by whether people agree or disagree with that Ensign Study earlier, if we say we're going to treat just those patients with pattern D, depending on which physician using the four different tests that came in, we'd be treating all different patients. And then if you go to your competitor down the line, one would take you off treatment.

So I think there still is confusion. I really would like to know the information in these intermediate patients, but I think we have to look at risk as inappropriate treatment. We

all do know we're under treating and missing a lot of patients, but I'm not sure we have the evidence to suggest we will be able to identify them with these methods.

DR. STEELE: Dr. Zhang.

DR. ZHANG: I will say this question should be answered by -- should be assay in a subclass lipoprotein specific. So in general, we're not there yet. And specific, for example, some of the LDL subclass could be used for -- I think this question should be to and when the beginning of the treatment. In other words, whether or not to such a subclass lipoprotein can be used for diagnosis. In other words, tell the patients that you should start treatment.

Second, whether or not the such assay or results should be used for monitoring clinical treatment, especially sub-communicable treatment. By the general criteria today, some patients should not be treated. But if you aid a subclass of lipoprotein, and if then you tell the patient, say you should start treatment,

then the question will be what clinical parameter you are going to use ethicacy or necessity or side effect such a treatment.

So I will say to this question is we don't have sufficient data to support either to convince a patient to treat, start a new treatment. Second, we may have a problem to tell the patients whether or not such a treatment you prescribe is really effective or necessary. And I will say we need more data.

DR. STEELE: Dr. Winter.

DR. WINTER: If the predominant use of the test, the LDL fractionation, is to decide if somebody should move from intermediate to more intensive therapy, they'll already be on therapy. So for that reason, I think that the benefits are likely to be greater -- equal to or greater than the risks.

DR. STEELE: Any other comments?

DR. MARCOVINA: I --

DR. STEELE: Dr. Marcovina.

DR. MARCOVINA: I agree with Dr.

Winter's comment. And also we need to consider that there are a lot of recommendation about the targeted LDL to 70 mg, but we don't have a strong evidence that there really is no risk in lowering LDL cholesterol to that level.

DR. STEELE: Any other comments? In some way I would think to say that the have split a little bit -- the panel is split a little bit in their opinion. Some felt that we don't have the data to show the value of this testing, and such there could be, because we don't have the date, then we could be treating and, therefore, there could be harm. There was another set of opinions which basically said that we should be using it -- or we could use this as a positive risk factor to get people into treatment.

DR. WOOD: How would the accuracy of these subfractions be established? What is an appropriate reference method, and what are appropriate acceptance criteria when comparing to whatever reference method is appropriate?

DR. STEELE: The question is open for discussion. Dr. Winter.

DR. WINTER: I think regarding the electrophoretic and VAP, that those should be compared to the traditional ultracentrifugation. In the absence of a predicate for NMR, that other NMR labs, totally independent of the founding lab, would need to exchange samples to begin to look at the robustness in more than one center.

DR. STEELE: Any other opinion? Dr. Remaley.

DR. REMALEY: Electrophoresis, of course, has been used for many years in clinical laboratory, and I think because the methods separate the subfractions based on physical properties, I think it's a mistake to try to get them to necessarily agree. They my each have value for different reasons.

I'm optimistic that, although, it is a difficult method, that because of our experience lab with electrophoresis, one can --

should be able to develop a system for establishing the accuracy of such methods in a professionally test program which exists for serum protein electrophoresis and for many other electrophoretic techniques we use in the clinical laboratory.

I think the NMR is clearly a distinct methodology, and I think that you will have to develop a separate accuracy based assessment for NMR and also for density gradient ultracentrifugation. Again, it's based on a different physical property and I think that in that case we do have experience with analytic ultracentrifuge, and I think then we have to develop a separate criteria for standardization of such methods.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I would say in the absence of outcome studies, which I think are really necessary, they should be compared with Apo B, and the LDL subtypes should be compared with Apo B and non-HDL cholesterol. And because

these are known to be the best regular markers we have, and there are outcome studies showing that, or at least many studies. And I'm not exactly sure of how good the relationship has to be, but I would expect to see something at least with R.9, and it's a tricky subject, but...

DR. STEELE: Dr. Zhang.

DR. ZHANG: Apparently, we could not get one set or one specific set of criteria for such a broad subclass for -- don't even talk about so many HDL LDL subclass. I think my opinion will be for well established method, for example, electrophoresis. And it can be tested or establish a certain standard, use standard GCP or GLP type method to validate the assay for that specific method. For example, as presented this morning for major different methods.

I think the industry should take a lead to at least present to the community, to the public, to see what do they think, what kind of good practice, good clinical practice or laboratory practice would generate reliable

data. You have to have a standard. So I think I should say the developer, whoever you call sponsor, they should know better than the public, than other investigators, about their product, their idea, they're science behind the products.

I think they should emphasize the standardization, not across the board, but at the least for that product, they should be a key for the future of such an assay. If you develop a sensitive and a scientific valid assay, but if you do not have quality control, and you can not ship it to a regular clinical laboratory to use it.

And no matter how fancy you can do you in you lab, but eventually it limits the use. So I think I would suggest to think about this question in the product or assay specific way.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: Regarding that what was just mentioned, I would say that -- and I

said well it should be compared with Apo B and non-HDL cholesterol -- and there are many, many studies, some perspective, others cross-section, what have you, that show that these are the best markers that we have right now for looking at Apo B lipoproteins.

But of course, outcome studies -- in many of these are outcome kinds of studies. And now I think if those studies are to be done, they should be funded, and I think this is what might have been referred to, they should be funded by the industry since they stand to benefit if it turns out to be the case.

DR. STEELE: Any other comments? I guess -- and to summarize this one is a little difficult. I don't think we really have a final answer. I think what was suggested was that the industry would have to take the lead in -- either by developing the, I guess, reference standard materials and to open up their methods so that they can be evaluated, and we'd be able to evaluate between people using similar methods

across laboratories.

And I think we acknowledged this is going to be a major problem, but I don't think we have a real good answer at this part. Yes, Dr. Winter.

DR. WINTER: I'd just add that as more labs are running these, for example, possibly with the Quantimetrix, that they carry out kind of a classical workshop where sera are shared among sites, and then the results compared. And that, in essence, truth may be just what is consensus at that point.

And that has to be done, again, when you don't have subfractions that you can measure out and dissolve in water, like creatinine or glucose.

DR. STEELE: It might be, and also possible that some of the proficiency organizations can get -- I think that was suggest by Dr. Remaley -- could get involved into this, and there might be an appropriate place besides the industries.

Obviously, everything else has been done in the lipid world by the government CDC, and I would hope eventually they would maybe be there. But I don't know -- I don't think, from what was discussed today, that they have any plans imminent to develop standards in this area.

Did the industry rep have any comments or, since we did suggest that they might be part of this process?

DR. WORTHY: I think it's a -- there would be a lot of value in having a -- some kind of a reference preparation that could be used, as well as a reference method. Now how that material is developed and how, what reference method is used, I think has to come out of, perhaps, a workshop of various scientists, both within industry and in academic medicine.

I certainly -- while it may be difficult to develop a reference preparation, I think every time we've had to develop a reference preparation for use in clinical

laboratory, it's been difficult, but yet somehow, over time, we've figured out a way to get it done.

And I -- while this may be particularly difficult, I'm enough of a cockeyed optimist to think that there's enough intelligence in the scientific community, that we can figure out how to get it done. And I think that opens up the whole area for standardization because once you have the reference material, you now can really talk about a reference method, and then start relating the various methods back to a, hopefully, a higher order of referencement.

Now, how that's funded, you know, I -- it's -- I think it has to be probably a joint thing. It's going to be very difficult for industry to shoulder the burden of -- of the entire cost of doing these studies. So I think somehow we have to figure out some kind of a shared responsibility for getting the work done.

DR. STEELE: So you're suggesting a

either professional or governmental workshop with all the stakeholders involved and coming to some conclusion, and at that point then how to prepare -- what should be a standard and how it should be prepared.

DR. WORTHY: Precisely. What -- the -- I guess the analogy that comes to mind is what has happened with hemoglobin A1C over the last 20-25 years. I remember going to an NIH conference in the early `80s, we were talking about reference methods, and the reference methods that were talked about in the `80s are not what is now the higher order reference method that's being used. And you had a variety of different methods of measuring glycolated hemoglobin from immunoassays to affinity to chemical reactions.

Somehow, everybody got together, put aside their vested interest, and came up not only with a standardization -- have reconciled the standardization in the United States with, to a large extent, with the standardization

outside the United States, but now have a higher order reference method.

So it can be done. I think we just need to get the right people together to get it done.

DR. STEELE: Thank you. Dr. Levinson.

DR. LEVINSON: I don't think this could be compared so easily with glycolated hemoglobin or TSH, which are things that have been well standardized because this is really a camash of different things. And, moreover, the methods as they are seeing now, don't agree very well with one another, I mean in any sort of way, whatsoever, as far as I can see.

I didn't see anything in the question about a reference preparation. It was referring to a reference method, I thought. And as far as a reference preparation, I don't know what you would do because if the methods don't agree very well with one another, that's a really big problem

DR. STEELE: Dr. Winter.

DR. WINTER: I'd like to encourage also that there be an exchange of samples between the different technologies to try to define what is meant by one technology with one set of labels versus another. Even if it's true that, let's say, density is more important than particle number or vice versa, I think it will be very helpful to look at all the assays to know, okay, this one sera, it's characterized in this fashion by this particular assay, how is it characterized in that fashion.

Not to say that anybody is correct or incorrect, but, you know, try to get everybody on a similar type of standardization. Now whether that can be done with NMR as far as nomenclature goes, I don't know, but for fractions, the biology is the biology. Now it could be an elephant, and we look at it from different perspectives.

You know, somebody is looking at counts versus size, but the biology is the

biology, and we should be able to somehow compare the methods one to another better. Which, if all four methods, let's say, are in long-term use, it's going to be really important because what will happen is the patient goes to Doctor A, he sends it to Athrotech, three years later they move to Florida and this doctor doesn't use Athrotech, or there's a change, let's say, in the insurance of the patient that gets sent to another center.

DR. STEELE: Okay.

DR. WOOD: Question 5. How should expected values be determined for lipid subfraction assays? Is it possible to make meaningful tests interpretations in cases where reference ranges for normal and disease patients overlap?

DR. STEELE: Dr. Remaley.

DR. REMALEY: I think I made this point earlier. I think this is a dilemma, but of course, this is a dilemma with our conventional tests. Unfortunately, we don't

have good diagnostic tests that segregate the baseline of disease and non-disease distribution. And I think the best way to interpret such data is given by ROC curves.

But in the first metric I think is looking at the subfractions compared to the case of HDL subfraction compared to HDL cholesterol over LDL cholesterol to the LDL subfractions. And I think many studies have shown that those tests are better. However, when you do it in a multi-varied analysis oftentimes, doesn't seem to be any added value. But not always. Sometimes those tests show value.

But I'd just like to make one more point about that, is that the use of algorithms, even for classifying patients with NCP, I think are very difficult. And I think most clinicians -- it's true that you can maybe get additional information by including the CRP triglycerides, but I think most physicians still interpret their results as independent entities.

And I think just because the

information is diminished by multi-varied analysis, does not necessarily their still not valued and using that test result because that, in fact, is how most patients -- how most clinicians use test results.

DR. STEELE: I have a question of the FDA. This question, part A, how should expected values be determine. Is expected, basically are we talking reference?

DR. WOOD: Yes. Reference ranges.

DR. STEELE: So that would be how we would define, I guess, our reference population to assess different aspect of the question.

Dr. Marcovina?

DR. MARCOVINA: For each -- the methods are incredibly different from each other. They are actually measured in or separating something different from each other. So each method should have data in a large so-called healthy population, but that also is not going to give us a reference range because we know that the good percent of that population

will actually be in the category of risk.

So all this is a very controversial situation, and I believe that each method actually has its own inherent problem that needs to be solved. And from where this point of reference is coming from to separate risk versus non-risk. We know how LDL cholesterol and HDL and total cholesterol were established by extremely large population based clinical studies, but we don't have any data for this method. So it would be a very difficult endeavor.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: This, again, is a difficult question. I would say that I believe the panel has decided that this should only be used in special circumstances anyhow, and it's still a little unclear which circumstances. And I agree with Dr. Winter, after the fact is not a good way to do it, but at least you can may be able to do something at that point.

So what we're really doing here, it

seems to me, is looking at people and then really stretching it to find something abnormal that we can deal with. And as such, I would say -- and in that the test don't agree very well with one another, that the reference ranges would have to be something, I guess, just devised by the manufacturer based on their experiences, unless they can go do outcome studies and show exact reference ranges.

DR. STEELE: Dr. Winter.

DR. WINTER: I think the expected values, if we're talking about populations, can be easily defined, but I don't think we want to define the target ranges, at least for therapy, based on distributions of the population because we know half the population is going to die of cardiovascular disease.

So if you take a NCEP approach, you'd say we should look at a population that has a low long-term risk for coronary heart disease and see what their subfractions are. Now I don't know if that means we take healthy

80-year-olds or we go to, let's say, genetically similar populations that have lower risks of heart disease, but I'd like to see expected values based on what we would consider to be healthy and not population distributions.

DR. STEELE: Yes. Dr. Shamburek.

DR. SHAMBUREK: No. I was just going to comment as far as a clinical view is, if we have a patient with coronary artery disease, we have certain LDL values. And I think everyone's eluding this. If you have a person with two risk factors, we have an LDL value. But now we're looking at an intermediate where they don't have risk factors and we're talking about a laboratory value.

And you were mentioning it, if we had two overlapping ones and, not that I advocate it, but if we look at pattern A and pattern B, do we go down the middle, do we go a little bit to the right so we don't over treat but we're going to miss people? Or do we go to the left so that we make sure we treat everyone

and not miss any?

And I think that issue will have to come up because I think most, if not all, that we have seen are all overlapping methods. And I think it's hard to say on a general category because I think these are such different techniques. I think each one will have to be dealt with individually because they're such different techniques.

But I think ultimately the clinician is going to want to know who do I treat. I don't want to know these numbers cut off. Give me the number who needs to be treated. And I think that's going to be a difficult decision. It's one I would like. I have many of those patients, but I think it's still the people who are experts at drawing those lines, you know, I think they're going to have to draw the line.

DR. WINTER: I think if we had the sensitive test and we have safe medications, you can argue that you'll go for sensitivity and not specificity. I mean if half of us are going to

die of cardiovascular disease, and we don't know who to treat, you'd say let's treat everybody, we'll potentially help half the population.

DR. STEELE: Dr. Watson.

DR. WATSON: I will agree that the real risk is in under treating and also defining something at which we know is going to be a moving target. I think just as we've done with LDL cholesterol, what we think of is normal today is not going to be the same thing as we think of as normal in five years. And I think that's the big challenge with this.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: As far as establishing the cut-off's, doesn't that have to be done though on a risk -- I mean this isn't a diagnostic test, this is a test that's assessing risk. So you have various values that -- and each of those values is associated with a certain risk, and then it's up to clinicians to decide what risk is now unacceptable to my patient. So your cut-off, in my opinion, would

be set on what value is associated with an unacceptable risk.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: Well it seems to me, if that's true, and I agree with you, that you -- the way we do that now by the National Cholesterol Education Program Guidelines is based on a vast quantity of information that's been collected from multiple studies, and so that would have to be done.

DR. STEELE: Dr. Watson.

DR. WATSON: Yes. You really need prospective population-based studies, and none of them really are. They're based on specific populations that have been looked at and they saw that certain people had higher risk. But really large scale prospective population-based studies are lacking.

DR. STEELE: Dr. Remaley.

DR. REMALEY: I think we have to keep in mind what Dr. Winter said, that the prevalence of course is very important in terms

of where you draw that cut-off, and we may not be able to have the single cut-off depending upon a risk, and then make it back to the art of practicing medicine.

And, again, people who have a higher risk or higher pretest probability, you would probably be more aggressive and lower the threshold. So I think it may be difficult to come up with a single answer for this.

DR. STEELE: I would agree with that answer. Any other comments? Dr. Winter.

DR. WINTER: I think unless you're looking at genetic tests where you know what the genotype is, there are few tests that don't have great overlap for common disorders, whether you're talking about blood pressure, or cholesterol, or glucose. So I think we're always going to be faced with the fact of sensitivity versus specificity.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I would say that even with genetic tests, there's something called

expression, and it varies substantially. So...

DR. STEELE: Dr. Loew.

DR. LOEW: It may be belaboring the obvious, but we certainly need a clear definition of truth here. What the FDA puts in quotation marks, the word diseased, then I think that's expressing, at least to me, the uncertainty about what diseased means.

And looking ahead to the next question, again, dyslipidemia appears, and from the point of view of a mathematical approach, if one is going to try to make decisions about true positives and false positives and so on, one needs a clear statement of what constitutes a positive and what constitutes a negative.

Now I think that's what this committee is grappling with, and perhaps there should be some discussion specifically about how to define things, at least from my point of view.

DR. STEELE: Dr. Winter.

DR. WINTER: Maybe to address this a

little bit is that the genotype and phenotypes are descriptions of lipid values that aren't diagnostic in and of themselves or characterized disease. On the other hand, if you say somebody has familial hypercholesterolemia, that's a recognized in born air where we know the natural history of the disease, and we know that there's going to be a bad outcome.

So with the lipid subfractions, if we have prospective studies from an early age that would identify somebody that has, let's say, high LDL number or small LDL, and that that is shown with a high predictive value to identify bad outcome, independent of other risk factors, then that might actually be a disease.

DR. STEELE: Anybody else? Well I just want to make a very brief summary here. I think for the expected values, I think it's felt that they should be derived from healthy people and not from population studies. The second part has been kind of a wide discussion, I think most people would agree that we need more data

to be able to define where we need to put cut-offs.

And that there was voice, though, the opinion that the risk cost benefit here allows us to put a value there, and since the risk of treating -- over treating people is probably not very -- is very small, that that shouldn't be a deterrent.

Dr. Gutierrez, do you have any other comments or do you need more from this committee on this issue?

DR. GUTIERREZ: At the risk of sending you off a deep end, let me just give you a little bit. So what I hear is that it's going to be, and what we've seen, is that it's very difficult to define a normal population and a diseased population.

There's a lot of -- there's -- we have a lot of overlap between the two. So I hear that we should be doing ROC studies. Then the question becomes, well should this be done in the specialist populations for which we

should be clearing this for, or should this be done -- it's a little unclear to us at this point where we would leave with that.

Should we be looking at a set of data to set up the ROC population? Should we look at -- what kind of data should be looking at since it is clear that, from the panel, that you think this test should be used for specifics as a populations. How do we set those cut-offs in ROCs? Do we need to look at those specific populations or not, or do we just let them set a -- well set essentially the normal population, and anything above that is interpreted how?

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I'm not sure how to answer that question, but it's just that -- and I go back to really what I said before -- since, in my view at least, the test would be used only in specialized circumstances where one is trying to stretch to find something that's wrong with the person, that the reference values could actually be pretty extreme values because then

you can be pretty certain he has -- maybe there is some kind of a dyslipidemia here.

So I'm not sure even that you would just want to look at any kind of normal groups, or I think you might be better off looking at diseased groups and seeing how extreme their values are.

DR. STEELE: Dr. Remaley.

DR. REMALEY: I think the dilemma for the diagnostic companies is that, as Dr. Winter mentioned, and it's a very highly prevalent disease. So if you're not careful how you define your control population, that'll diminish the apparent utility of the test because you'll have, of course, possibly people went in the control group that have disease.

So I think the answer is you do the best job that you can and if you see -- whatever way to find your control population, and whatever test you use, if you see, again, using a ROC curve, some advantage, I think that gives you some assurance that there's some value. And

I think it's probably likely be an underestimate because, again, the problems diseased in general populations, it's hard to weed those people out from the control group.

DR. STEELE: Dr. Worthy.

DR. WORTHY: Just very briefly. I think we need to take the various manufacturers into this process. They know as much or more about how their test performs as anybody. And before we decide that we should use Receiver Operating Characteristic curves and things like that, we have to make sure that the manufacturers are part of the dialogue and we get their input. They should have very good input and direction to answer some of these questions.

DR. STEELE: Dr. Winter.

DR. WINTER: As the subfractions -- we get more data how they're correlated with various risks, you can take the analogy of glucose, where at a certain glucose level, you have a significantly increased risk of disease

because certainly these are continuous variables. So as the prospective studies are done to define those, that may very well lead to what, either particle number or LDL density number, what have you, that there's a significant increased risk in that your curve of whatever value you're measuring versus risk is really taking a turn up. And that's been the ADA's approach to redefining what a elevated fasting plasma glucose is.

And then you can very well have a grey zone as well, equivalent of impaired fasting glucose or impaired glucose tolerance.

DR. STEELE: Okay. Excuse me. Dr. Levinson?

DR. LEVINSON: Yes. Just one other thing though here that maybe should be mentioned, and that is in regards to lipids, the National Cholesterol Education Program has actually determined cut-offs that are far below that which, at one time at least -- now, maybe

everybody practices are on a lipid lowering drive, but at one time, at least, was certainly not 95 percent of the population. I don't know. Maybe it was 20 or 30 percent. Okay, so, you know, that's an added feature that has to be considered here.

But again, as I mentioned before, that I think since they're looking at this point for extremes -- and I do think, as mentioned, the company may have to have a lot of input into what they consider abnormal in these selected cases.

DR. STEELE: Okay.

DR. WOOD: I guess I'm ready to go. I jumped it up to Question 7. Question 6. If used either as an adjunctive test to traditional lipid measurements, or as a stand-alone diagnostic to diagnose or predict risk for dyslipidemia or atherosclerosis, does the lack of standardized nomenclature or differences in assay performance, such as reference ranges, precision, fractions analyzed, etc., pose an

unreasonable risk to the patient?

DR. STEELE: Well I'll start with Dr. Winter here. Oh, we're not polling. I'm sorry. But I know he's got an opinion.

DR. WINTER: From the data that was presented here, and the lack of correlation at least, based on phenotype A versus phenotype B, if patients were not to have the same assay run long term, there could be definite confusion, and I think mis-diagnosis and mis-treatment.

DR. STEELE: Any other opinions here? The day's getting a little long here. I think that Dr. Winter's comment was also brought up by Dr. Tsai, and I think that that's the main concern is the confusion that all these various methods might cause, and people switching back and forth between methods. And that could cause at least anxiety in the patient population, and could lead to some problems.

Yes, Dr. Grines.

DR. GRINES: But I see a similar thing with measurement of C-reactive protein and

homocysteine. Depending on the lab, there's totally different ranges that they consider acceptable, and so you write patient a prescription to get some blood work drawn, and they come back with a lab value that is very different compared to the last measurement. So it's not just with this particular test, it's the whole industry.

DR. STEELE: Well, excuse me, but I think -- I know Dr. Winter is involved with this a little bit more, but the -- those values, as I understand it, should be the same.

DR. GRINES: The normal range --

DR. STEELE: Oh, the range is normal ranges. Okay.

DR. GRINES: They are totally different --

DR. STEELE: Okay.

DR. GRINES: -- and apparently they're run by different assays, I would assume, otherwise the ranges are different.

DR. WINTER: I think as far as CRP

goes, you have to be very careful does the patient have coexistent infection because it can usually be elevated because of that. And I think the NCEP is pretty clear as to what a desirable high sensitivity CRP is versus an elevated CRP.

The other issue is that not all CRP's are created equally. If you go back to the titers of CRP that are run in micro, if you just ordered CRP and got one of those, you'd really get a much different result. Homocysteine, there are pre-analytical factors that affect that. The sample, if it's appropriately treated pre-analytically, would be centrifuged and separated very shortly after the time that it's drawn.

So I think the laboratory community, we have a responsibility to make sure that we treat those samples correctly. On the other hand, if a sample is drawn in a physician office lab, it sits maybe at room temperature for a few hours, you get a break down of protein. So I

don't know that it's the analytical issues so much as the pre-analytical, but as laboratorians, we're responsible for all those levels.

DR. STEELE: Any other comments here?

DR. TSAI: Yes.

DR. STEELE: Dr. Tsai.

DR. TSAI: I think the lack of standardized nomenclature is not something that is so serious that would prevent these tests from being used, but certainty is less than ideal. And in addressing Dr. Grines' comment, you're talking really different levels of concerns.

So one is you're talking about really sort of between laboratory precision and accuracy. The other is now we're talking about totally different nomenclatures. So I think it's not quite the same, but I think it's livable.

DR. MARCOVINA: Well I believe that

by knowing that the tests are so different, the manufacturer, and up to this point in time, the manufacturer coincide with the laboratory's measure in this test. They should be very rigorous in defining the values they are providing as indicator of risk because they provide interpretation of their values, and I believe that they should be very vigorous in how they arrived to the interpretation of the values.

DR. STEELE: Dr. Gronowski.

DR. GRONOWSKI: I think standardization would be optimal. If not, then we need - I think Dr. Watson alluded to it earlier, that we need significant patient education -- physician education because as Dr. Winter said, if you go from one physician to another, you change methods that could have a severe impact.

Of course -- I mean Dr. Grines pointed out this is true of other tests, and that's true, we know that. But for certain

tests where we know that, then patients are re-baselined when they're retested on a new method. You know, you go off on of your insurance and you go to a new method, then you re-baseline, measuring the old and the new.

And that would -- if these aren't standardized, then physicians would need to know that if you're going to switch from NMR to something else, then perhaps you need to re-baseline and look at their values on the old and the new method.

DR. STEELE: I think we're in agreement that there's plenty of chance for confusion here. And the question, I think, is how best forward to go -- to attend the confusion, whether that be a workshop with all the stakeholders under the guise of a professional organization or a government, I think is what's needed.

I think -- and if that doesn't happen, there will be problems and continuing confusion, and I think would weaken the area

actually. The area would do better to have a standard nomenclature and such.

Yes, Dr. Levinson.

DR. LEVINSON: I'm not exactly sure if the question means the number of particles in a particular size. Is that what it means? That is, I understand -- it says, is there a difference in the assessment of lipid subfractions based upon particle size versus particle --

DR. WOOD: Wait. That's the next question.

DR. STEELE: We haven't gotten there yet.

DR. LEVINSON: I'm sorry.

DR. WOOD: Apparently you're ready to go too.

DR. LEVINSON: Yes. I -- no wonder I was confused.

DR. STEELE: Okay. Yes, please. Go ahead.

DR. WOOD: Question 7. Is there a

difference in the assessment of lipid subfractions based upon particle size versus particle number? If so, what are the strengths and weaknesses of each method? Please discuss.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: I -- then I'd repeat. I'm not exactly sure what's meant there. I assume we're talking about particle number of the subfractions after we decided on the size. Is that right?

DR. TSAI: I guess. I'm sorry. Is that okay?

DR. STEELE: No. I think it's talking about the issue of the NMR versus the other methods. Is my understanding...

DR. WOOD: Yes. What we're asking actually is is there a difference in assessment of the values if you're determining on values, you know, where the result is due to particle size, as opposed to a result that's due to particle number.

DR. STEELE: Dr. Tsai.

DR. WOOD: They're different methods.

DR. TSAI: So I mean before -- before just answering, maybe just for the clarification of not everybody's totally clear about particle number versus particle size. And to reiterate the fact is that particle numbers provided by NMR is the number of particles. And typically the other methods have so far offered particle size.

Now then, this creates, you know, a bit of confusion, even among the connoisseurs from time to time. And I'm in the midst of writing a paper and there are a lot of connoisseurs who seems to misunderstand from time to time.

I get the impression, though, that -- and I'm not sure that really the particle number can be derived, although not exactly, from the average size times let's say in a case of a gradient gel electrophoresis, the density of each band.

So that, although currently the particle numbers only provided by NMR, I think an equivalent type of medal can be reached by other methods such as gradient gel electrophoresis. And I could be mistaken, so...

DR. STEELE: Any other comment?

DR. SHAMBUREK: Yes. I think that's a very good point. I kind of refer back to the slide or the cartoon several people made of the scale, and they showed LDL particles on the left and on the right of the scale, which was balanced, was a number of small LDL, which was increased in number and presumably increased -- and were smaller in size and increased in density.

And we've heard a lot about that. We're looking at several methods and trying to say they're the same. But I think we're measuring different properties, and I think certain techniques measure size better, certain techniques measure the number better. And I think if you really want to say which is better,

they might both be measuring the same end point, which is a patient at risk.

But if you really want to know for sure, you're going to have to go back to these studies and have NMR go against gel on the same patients, and there are a few of those. But I don't think head on head they're trying to do that. And in that sense, you're going to really show one is better than the other.

I think each one -- one might measure size better than it will do number, and another may do number better than size or density. So I think their measuring different things and I'm not sure we could say this is better than that unless you have larger head to head comparisons.

DR. STEELE: Dr. Winter.

DR. WINTER: I'd just like to reemphasize you're point and -- that I had asked Mr. Wood earlier if there were studies that compared the assays head to head, and there weren't any. I think to find out if there is a

superior assay, we have to compare them in the same population to determine if one of the assays is more predictable than the other. So I don't think we have the data to answer this question.

DR. STEELE: Dr. Remaley.

DR. REMALEY: Perhaps this is a minor point, but I think one thing that's important to keep in mind interconverting is that both these methods assume that you have spherical particles, and that's largely true. But in the case of HDL, there's a significant fraction that's discoidal, and there's actually evidence now that LDL is ovoid in shape.

So I think that makes it difficult because the different methods were affected also by the geometry of the particles, and I think a lot times, if I understand it correctly, the particles are based on the mathematical calculations assuming a spherical particle.

So you might have some differences related to the underlying physical structure of

the particles.

DR. STEELE: Dr. Levinson.

DR. LEVINSON: This is a very good point that Dr. Remaley makes. Oh. This is a very good point that Dr. Remaley makes. And also it's still not always entirely clear, even with LDL, the exact shape of the particle.

So, and the other question that I would have, if these methods are encouraged, then there's apt to be other methods that would come out, and they may measure different other facets. So wouldn't our conclusions regarding this be premature in that sense?

DR. STEELE: Any other comments? No. Well I think this is easy to sum up. I think it's basically we don't have the data to make that decision, and it needs a head to head type study.

I think that concludes our meeting here. One thing I need to ask Dr. Gutierrez, any comment?

DR. GUTIERREZ: Let me just make a

quick final statement. I want to thank everybody in the panel. This is really helpful. It helps our decision-making in a major way. Thank you very much.

DR. STEELE: Thank you. And, Dr. Gutman, any comments that you would have for the panel or the participants? And Dr. Gutman is the office director of ...

DR. GUTMAN: No. I appreciate the attention you've given to this very important topic, and I actually appreciate both the diversity of opinions and also your ability to actually create some order among them. So I particularly appreciate your help. Thanks.

DR. STEELE: Okay. And is Don St. Pierre here? No. Okay.

With that, I want to thank all the panel. I want to thank all the staff of the FDA for the assistance that they gave us today.

And with that, this meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel is now adjourned.

(Whereupon, at 4:21 p.m., the above-entitled matter was concluded.)