DR. MOORE: Can I have the frozen section slide for LMP tumors? When you say there's --

DR. LEVY: Well, remember, you guys were doing this at a GYN oncology center --

DR. NETTO: Correct.

DR. MOORE: I'm actually showing you data --

DR. NETTO: The 5 percent is a concern --

DR. MOORE: -- published data, not our data. When we look at -- slide up, please. When we look at all the data from across the country, it really is variable from site to site. And you can see the percent of LMP tumors that get upgraded on final pathology ranges anywhere from 7 percent up to 27 percent. But, as you see, we've gained a bigger understanding of LMP tumors in the last ten years. I would say that every LMP tumor ten years ago would have been staged. In this day and age, we don't because we have a wider understanding of LMP tumors.

And if you look at Kerman's data and his philosophies on the origins of ovarian cancer, we now realize that there is Type 1 and Type 2. And the Type 1's fall into a line where you go from a nonmalignant tumor into a pre-malignant cancer like an LMP tumor, and that's exactly what it is. They're not invasive cancers. And then they go on to become

invasive tumors.

And so in this day and age, the rate of having a false negative frozen section is really around 7 to 9 percent in most centers. And if you have an LMP tumor and you didn't stage them, that's they're final diagnosis, that's they're final diagnosis 90 percent of the time. They're not going to need chemotherapy and they're not going to need further treatment. If you notice in our study, only half of the LMP tumors were staged.

DR. FREEDMAN: Let me follow on in this question.

DR. NETTO: Go ahead.

DR. FREEDMAN: I think we accept that the earlier you can diagnose ovarian cancer the better, the better the outcome, the better the survival. I think everyone understands that. And we know we've got subgroups within that. And LMPs are considered one of the subgroups. And we've been trying to make sure that patients are adequately managed whatever stage they are in their disease whether it be early or later stage. And we accept the fact that somebody who has expertise needs to make the decision how complete a staging to do in these cases.

If you allow that decision to be made out in

the community, there is a danger there that these patients will be -- who should be adequately staged, patients who might end up having invasive implants, for example, you can't diagnose that with any test prior to surgery, and there is no way of knowing what you're going to find in these patients until you get in there, as you know. So it's important not to -- I think we've heard this talk about retro shifting of patients. If we shift more patients back into the community where there is less expertise, we have to consider the risk, the potential risk from doing that, that patients with either LMP with invasive implants or patients with early stage ovarian cancer may be under-staged and then -- not end up with a treatment that -- or the monitoring, even, that they should get.

DR. MOORE: They're --

DR. FREEDMAN: I mean, that should be a concern.

DR. MOORE: And I understand that point. If we look at the population of ovarian cancer patients now, over 50 percent of them are having their surgery in the community. And we need to do better. We need to do better for these patients.

DR. NETTO: But we've addressed that in the morning.

DR. MOORE: Okay.

DR. NETTO: This test does not resolve that issue, correct because these are already -- I'd like to see the consumer representative opinion, any discussion on that?

MS. LONDON: I would feel as a consumer I would want to be given the best information that I could from my doctor, and if I had been to my community doctor or gynecologist for a long time, I think I'd have the confidence there and I'd want a choice of whether I could go to the center or not as a consumer. Did that answer your question?

DR. NETTO: In general.

MS. LONDON: Or no?

DR. NETTO: Not just on this point. If you have on any other discussion about the test --

MS. LONDON: I have one for later if we're going to make comments. It can wait for later.

DR. NETTO: Sure. Okay. The industry representative?

DR. BRACCO: Yeah, I think -- and, again, I'll discuss this later as well, but I believe with -- I agree with Dr. Levy that the intended use as it's written right now -- and I understand why FDA asked for the changes they asked for. And, basically, what they

tried to do was compensate for what they believe to be a lacking part of the study population to be addressed in the intended use of the product, which I don't think is a prudent decision. I think there are other ways to address limitations in the study design or the study population, and that's by adding additional limitations to the labeling or other information that defines very clearly that there are some limitations in the study population.

But I think what we're faced with right now, and I think this is what's causing a lot of the angst here, is that the intended use is confusing because we tried to address a limitation and the population in the intended use, and I don't think that should happen. But, again, we can discuss that later once we go over some of the questions.

DR. NETTO: All right. Thank you. Dr. Lichtor, any comment, any discussion?

DR. LICHTOR: Well, I guess, I mean, the thing that bothers me most is the intended use. And I mean, I think as a test for evaluating patients, it does seem to add a little to what is currently used. I don't like -- it really bothers me a lot actually that the indication is basically, the way I read it, the indication is to triage patients to appropriate

specialists because, to me, that creates monopolies and is bad medicine. I think that the various doctors should know their limitations and may use a test like this to decide whether they want to refer or not, but I don't think it should be written in there that the goal of this is to refer patients to GYN oncologists.

That's what bothers me, not the test, all the issues with it. To me, it helps a little in terms of the diagnosis, and I think that can be used however you want to use it. And that part is okay, but I really don't like the wording in the triage issue. I think that needs to be addressed.

DR. NETTO: Thank you. Dr. Julian, since you're going to be in the crossfire at some point?

DR. JULIAN: Well, all I can say is that with all due respect, a gynecologic oncologist can offer any of these patients a world of options that a regular gynecologist cannot. I am not a gynecologic oncologist. Okay. I'm a regular gynecologist. Anything that suggests triage of these patients away from gynecologic oncology, in my opinion, is a danger, okay? They are the finest surgeons in our specialty.

Ms. Holland this morning told us that somebody in her community had ordered a CA-125 and ignored the result. In my community, nobody goes to

surgery without a CA-125, but they still don't know how to use it because it's not for that indication. I don't know that from the data this morning presented. I'm a real simple child of God, statistically, here. But, to me, two statisticians arguing about whether this test is any good or not really puts some doubt in my mind how useful it is under any circumstances when we already have guidelines that aren't being followed by the general gynecologists in the community.

If they followed the existing guidelines by any one of these methodologies described here from the imaging whatnot, there wouldn't be half of these patients being done elsewhere. So I don't know how that fits into the discussion, but I certainly believe gynecologic oncologists should handle these patients by any means necessary. But the difficult part is going to be getting the people that have ignored this since 1981 to all of the sudden wake up and use something correctly.

DR. NETTO: Thank you. Anybody else from the Panel? Go ahead.

DR. LEVY: I've got --

DR. MOORE: Can I just address that for a minute, and I assume that you're referring to the ACOG guidelines, which, you know, help us decide who gets

sent on to GYN/ONCs or stay in the community. Is that what you were addressing?

DR. JULIAN: Well, to me, it's actually sort of confusing because they will -- in any review of this material that supposedly has gone before them, they will say that you should not use this CA-125 as a thing for referral and routing, but, yet, as you well know, Gostaut and Weber did publish some guidelines that do appear in one of these -- it's not the --

DR. LEVY: Technical bulletin.

DR. JULIAN: Technical bulletins.

DR. MOORE: Yeah, yeah.

DR. JULIAN: It's one of the other advisories.

DR. MOORE: Yeah, it's --

DR. JULIAN: It's for an opinion or whatever it is.

DR. MOORE: Can we bring the slide up?

DR. JULIAN: But they're in the system --

DR. MOORE: This is what I assume that you're talking about is the ACOG referral guidelines or committee opinions. And you can see in here that they use a CA-125 level for pre-menopausal of 200 along with a number of clinical factors, and in the post-menopausal group, it's 35. Now, Deer King (ph.) in

Minnesota did a very nice analysis of this in patients that presented with a pelvic mass, and can you bring up the slide --

DR. JULIAN: You mean Wisconsin?

(Laughter.)

DR. JULIAN: Oh, I see.

DR. MOORE: No. Up slide -- no, the previous slide that you had there before with the Deer King results. So Deer King in Minnesota looked at the ACOG referral guidelines, and, hopefully, we can get that slide up. Up slide. And when they looked at the ACOG guidelines, we see that they had an incidence of 34 percent with Stage 1 to 4, and they had a sensitivity of 91 percent and a specificity of 63 percent. And then, you know, when we put ours beside theirs, you know, you can't do a direct analysis with that because it's not the same cohort, but we're achieving higher sensitivity and specificities.

And when Deer King looked at Stage 1 and 2 -- up slide, next slide, when they looked at Stage 1 and 2, we now see the sensitivity falls with their triage guideline, and this is what our college supports, down to 74 percent and a specificity of 64 percent. And in that same patient, you know, stage, Stage 1 to 2, we see that we compare much, much better than what we see

is being used clinical by our OB/GYNs, and this is really the only data that we have currently --

DR. LEVY: And if I could see the ROMA criteria applied to a general gynecology population, which is what Deer King did, I would be thrilled. That's what I really feel like we need to see because reality is that that is how this test will be used. I mean, that's what we really need to see is the performance in that same cohort so this is comparing apples and oranges.

DR. NETTO: Correct.

DR. LEVY: The ROMA is being used --

DR. NETTO: How can we compare that?

DR. LEVY: -- in a GYN oncology referral population.

DR. MOORE: This was a referral population as well. It's the same. It was the Mayo Clinic that looked at it, and they actually looked at both their referred population and their local population, and this is what we looked at. And I bring this up just because this is what we currently have.

DR. NETTO: It's actually --

DR. MOORE: And that's what you were saying. There is a whole spectrum of what we do right now, and I do wholeheartedly --

DR. NETTO: Was a formal comparison between the two populations done in terms of being the same population because I'm a little bothered by putting these figures next to each other not knowing what the qualities of each population is. Just because a patient is treated in Mayo Clinic and it's as famous as Harvard doesn't make these two populations the same.

DR. MOORE: No, but when --

DR. NETTO: Correct?

DR. MOORE: -- you looked at the inclusion criteria in the --

DR. NETTO: So that's my question. Did you look at this --

DR. MOORE: We did look at that in the --

DR. NETTO: So did you show us the data where there is significant or no significant difference between the two populations? Are they exactly the same?

DR. MOORE: We didn't go ahead and do those analysis.

DR. NETTO: Okay. Then, no, yeah.

DR. MOORE: Right. Thank you.

DR. OZOLS: Why couldn't you do ACOG and your study?

DR. NETTO: Correct.

DR. MOORE: You know, that is a good question. And the reason that we weren't able to do that -- can you bring up the ACOG recommendations again -- is that there is such huge variability in a physical exam and there was some data that just wasn't captured, you know, as, you know, such as -- slide up, please -- such as the fixed or nodular mass on the physical exam or the physical exam part of this just wasn't captured in our database. So I didn't feel comfortable using the ACOG reference guidelines. So we went with a more objective test that is being currently used, and that's the RMI that we talked about this morning. And we did do direct comparisons with that in our own study cohort.

DR. NETTO: Yeah, the only difference in that was the imaging, which you said it was very subjective.

DR. MOORE: Imaging can be subjective, yes.

DR. NETTO: Yeah. So my question is, which bring us to the question is, why was not the clinical data captured? If you're recommending a test even if it's being a standalone, to be interpreted in light of the other clinicopathologic parameters, which is a no-brainer for any test, and that's what you stated in your recommendation, why wasn't this data captured although it was supposedly part of the secondary

objectives? And if it was, why is it not discussed? Why wasn't it discussed?

DR. ALLARD: Well, let's start at the beginning. The purpose of the pivotal trial, the multicenter trial was, in fact, to validate the ROMA algorithm. It was not to validate imaging or other modalities. It was to validate the ROMA algorithm. So it was designed to capture the data that was necessary in order to do that. We did, in fact, capture imaging data. And the imaging data was used by Dr. Moore and his colleagues to look at the RMI and to make that comparison.

What we didn't have was all of the data necessary, as Dr. Moore has just pointed out, to do the ACOG referral guidelines primarily because of the one component there, the fixed or nodular mass. That just wasn't always -- that wasn't something we captured. And it was because it was not an intent of the trial to compare to imaging. It was to validate the performance of the algorithm.

DR. BERRY: Is it possible that you mis-coded the imaging? I mean, what you got, and it's really crazy, you got that the adding imaging to CA-125 makes it a worse test.

DR. ALLARD: Well, that --

DR. BERRY: And so, I mean, if you were building a model, you would never do that. You would instead of the coin coming up heads, you would say it came up tails because it's that particular imaging category is, in fact, indicating bad things. So it doesn't make sense.

DR. ALLARD: I understand the confusion, but let me explain that because there is a very good explanation for that. They're very different analyses. So on the one hand, you're analyzing CA-125 with a specific cutoff, and I believe the Agency used 30 and 60 were the CA-125 cutoffs. RMI is done very differently, and if we could have that slide up, please.

This is something Dr. Moore showed this morning, but it uses the imaging score, and it uses the menopausal status, and it multiplies it times serum CA-125. And what you can see there -- and the cutoff that we wound up using in order to obtain 75 percent specificity was somewhere in the 80s. I've forgotten exactly what the number was, but it was in the 80s.

And what you see, then, is you could clearly have a CA-125 level that might be positive but would not be positive in the RMI because of the cutoffs that are used. So they're very different methods. And

because of the differences in those methods, you can clearly see differences in the results.

DR. OZOLS: No, presumably, Jacobs built this on a database, and the database, if in fact it would have gone in the direction of your study would have been instead of U=0123 -- 13, it would have been U=310 because that would have been better. So there is something basically different about his database than yours.

DR. ALLARD: Although in the published studies that have validated the RMI, and there are several of those, the results look very similar to the RMI results that we show. They are very similar to the published data.

DR. SKATES: So just to add to that, it's very possible that the form that they used for combining CA-125 and imaging isn't optimal, and that is the reason decrement. If you don't combine biomarkers or multiple tests in an optimal fashion, you can actually decrement the results of the combined analysis compared to a single analysis alone. And that could be the case here.

DR. NETTO: Dr. Kondratovich, would you like to comment on this?

DR. KONDRATOVICH: I think that one of --

that imaging was available only for 80 percent of subject. But from other point of view, my understanding is that you used serum CA-125, which collected in this study, yes? Yes. So for particular pre- and post-menopausal group, this value is constant. And we used the same level of specificity because usually, like, if you have the same level of specificity -- let us compare the test, how they perform. If they have the same level of specificity, what's the level of sensitivity? And we see that it behave relatively strange. Why? It's difficult to tell. Maybe because its population is really different and it should be different RMI index for this particular referral population.

But my point was that we really need to have clinical data, how it was evaluated without ROMA test because this is some kind of information which probably related to the real-life clinical pre-surgical evaluation but cannot completely be considered like clinical evaluation because we see that there are some problems with this RMI.

DR. NETTO: True. So what you're saying is the RMI, by the nature of it being such a calculation and showing surprising directions compared to CA-125 alone probably --

DR. KONDRATOVICH: Yes.

DR. NETTO: -- is not the best clinical surrogate to compare this test to as --

DR. KONDRATOVICH: You're absolutely right. You're absolutely right. So this is something like we decided, like, yes, we need to have clinical, real information, pre-surgical. What was assessment of this patient based on the all available pre-surgical information, and this RMI, it's probably it cannot serve very good --

DR. NETTO: Bad choice --

DR. KONDRATOVICH: I cannot -- in general, maybe this index is working in some situation. But definitely, in this study, for this particular population, we see that, yes, you are right, it's surrogate and probably has a lot of drawbacks. Like, even don't use any imaging, use only CA-125. Your performance is even better.

DR. BERRY: Flip a coin.

(Laughter.)

DR. NETTO: Thank you.

DR. BERRY: Don't use imaging. Flip a coin.

DR. BECKER: So we would recognize and have some reservations about the completeness and rigor by which a comparison of the ROMA analysis to either the

ACOG or the RMI analysis might be considered appropriate. And it just leaves us back to the original question of for the test as it worked in the intended use population, okay, do the performance characteristics match up with what one would consider safe and effective because I don't know that we have the ability to come to a clean consensual agreement about exactly how the test matches up against RMI or how it matches up against ROMA. None of those analyses were pre-specified. And, to a degree, some of them are not complete. So there are holes there that need to be --

DR. NETTO: Can you speak up, please? Can't hear you.

DR. BECKER: -- moved past.

DR. NETTO: Thank you. Any comments from the Sponsor? Okay. Yes?

DR. OZOLS: Yeah, I still have, you know, three issues that there were -- many of us. You know, I am persuaded by the FDA analysis that CA-125, if it's not -- if ROMA is better, it's not much better. And I agree with my colleague that if two statisticians are arguing about the statistical significance from tests, it's probably clinically not much different for -- as a clinician, I say, you know, if you guys can't agree

that, you know, it's statistically significant, I really doubt whether it's going to be clinically beneficial. So we're talking about a small number patients potentially benefiting, very small number.

I'm concerned about the intended use population. I'm very concerned about sending back, triaging back a pre-menopausal woman who is "low-risk" back to her gynecologist. First of all, I don't think it'll happen much, but if it does happen, I think there is a potential for harm, that she will not get the best operation that she would have had if she stayed at the cancer center.

And I'm also concerned -- this also was pointed by colleagues -- that if this test is approved for this specific, again, very small population, who are already referred to a cancer center, it will be used all over the place, and it will be used in ways that you can't even imagine. And there's a potential risk of that.

I can foresee a situation where a woman has a slight elevation CA-125 and some other abnormality, and her doctor does this ROMA test and says, "Don't worry about it. You're at low-risk," and doesn't do anything. I mean, you know, there are -- and where this test never was even tested in that population.

It's like when CA-125 first came out, you know, 20 years ago, some people -- lots of patients had unnecessary operations just because their CA-125 was elevated alone. So these tests, they get a life of their own, and, you know, they will be used extensively by -- and perhaps in a harmful manner.

So we're really stuck with a very small patient population that were tested in that is not perhaps relevant to the community. And in that population, the benefit that exists is small.

DR. NETTO: Thank you. Go ahead, Dr. Skates.

DR. SKATES: Can I just respond to this --

DR. NETTO: Sure.

DR. SKATES: -- idea that because statisticians debate about particular statistical tests, therefore there is no value in the clinical scene, I think that's really jumping to an unwarranted conclusion, with due respect. There was evidence -- one of the issues that I -- one of the points that I neglected to make was that we actually had a range of specificities in our pilot trials. It ranged from 80 percent to 90 to 95 to 98.

DR. NETTO: And none of them were 75.

DR. SKATES: And it wasn't 75 percent, that's true, but it was down to 80 and --

DR. NETTO: Why not? Why -- didn't do it retrospectively? When you found out that 75 percent was your --

DR. SKATES: So in retrospect, we could have gone back to do that, but --

DR. NETTO: Because that would answer -- if you're saying the pivotal study is not powered to show the comparison in the subset analysis, and, clearly, we have huge concern about the subset, pre-menopausal. And so if --

DR. SKATES: Well --

DR. NETTO: Why wasn't it -- if -- was the pilot powered enough to show these subsets?

DR. SKATES: The pilot was powered to show a difference between CA-125 and CA-125 plus HE4. We didn't --

DR. NETTO: But not at the 75 percent? I mean, the problem is --

DR. SKATES: And --

DR. NETTO: -- it showed the difference in the range, dynamic range. That's probably not clinically useful. So the question, if that's the intention of use, why not go back and look at it --

DR. SKATES: We can go back, and we will do that now that we know that that's such a crucial issue.

The point was that we convinced ourselves that HE4 added to CA-125 with the pilot study. Then the question was how do you combine it. Once we figure that out, how do you validate it. And what we showed was the validation.

And this is -- and it was primarily because there is no indication, no approved test for this indication that we didn't compare it to CA-125 alone, all right? So that's why we didn't think it was a point to really focus on. And what we wanted to do was validate the test that we came up with for this indication.

DR. NETTO: And that's exactly the point about knowing that once the cat is out, the CA-125 is not even approved for this, and it's ACOG, first one on the ACOG list on how to refer. So it will be very hard for the gynecologic community doctor not to look at this sexy test that is being used by the gynecologic oncologists who decide who is going to go back to them, not to use it at initial. So that's why we're extremely careful in the wording, and I hope you understand that.

DR. SKATES: Absolutely. And we're, you know, very open to, of course, any Panel's recommendation about wording and adjustments to that.

DR. NETTO: Dr. --

DR. LEVY: I mean, yeah, from a clinical standpoint, the relevant questions are refer/don't refer, operate/don't operate. I mean, those really are the key decision-making issues for patients. So we've already taken away both of those decision points in the labeling for this test. I mean, the labeling says it's already patients who are referred and already patients who are going to have surgery regardless. So we've taken away the clinically relevant decision points.

DR. NETTO: So you're saying what's the point, then, by doing the test?

DR. LEVY: Exactly.

DR. BRACCO: If you go back to the original labeling submitted by the Sponsor, you can see it actually says women presenting with an adnexal mass who are candidates for surgical intervention. And then all these concerns, as I said earlier, could be listed in the labeling, all of those limitations, however FDA wants it.

DR. LEVY: However, they weren't -- this test wasn't evaluated in that population of patients --

DR. BRACCO: That's right.

DR. LEVY: And we don't have any data on which to make that decision.

DR. BRACCO: That's right, but it's clear if you put those limitations around the intended use that I think is --

DR. LEVY: But we don't have any data to present the clinician how to analyze and result because we don't -- haven't tested it in that population.

DR. NETTO: Understood.

DR. JASON: Let me also raise -- the concept of creating this algorithm is very appealing. But one concern I'd have is I think you do have data that suggests that this new assay does add something to a certain group. The question is, will that algorithm -- is the algorithm going to make things less clear to the clinician if perhaps just straightforwardly presenting the possibility of some combination of these two assays might be useful in certain settings. Would that be a clearer approach rather than having someone just blindly enter data into the algorithm and not really understanding what it is they're doing with that especially if we get down to the general practitioner?

And I think in a referral center, they're probably sophisticated enough that they don't need an algorithm because they can weigh these parameters themselves. And are you in fact potentially in centers other than the ones involved in this study creating a

false sense of absolute that I can say you have an 11 percent chance, when in fact it may be 15 percent or 10 percent or 5 percent? Would you not be better, potentially, as appealing as this is, to simply do it in a more straightforward way?

DR. SKATES: So I think one of the responses to that is that what gets sent back to the physician is the CA-125 value, the HE4 value, and then the Predictive Probability if the patient is pre-menopausal and the Predictive Probability of the patient is post-menopausal. That is then left to the clinician as to which part of that information whether they want to use it all or only part of it to use. So they could weigh it one way or another. But what we have data on is what that particular combination that we came up with will give in terms of the upgrading characteristics --

DR. JASON: Now, will you be specifying --

DR. SKATES: -- in terms of the sensitivity and the specificity.

DR. JASON: And will you have in that insert that this is based on a study done on this population and give those --

DR. NETTO: With a lab report because that's another issue. See, if the lab report is going to come with a cutoff for positive HE and cutoff for positive

CA-125 and a PP, would the lab report indicate that we don't know what the significant of this HE4 positivity means? You cannot use it by yourself? Because that's a little -- what you just mentioned is a little concerning. If --

DR. ALLARD: No, let me explain the way that it will be presented to the clinician and how we believe that they could use it. It will be presented, as Steve just mentioned, they will get a CA-125 result, an HE4 result, and they will get predictive probabilities for pre-menopausal or post-menopausal. Of course, it's up to the clinician to determine is this woman pre or post-menopausal.

And then, in fact, in terms of how they implement it, what we've added to -- thank you. Could I have the slide up, please? What we've added to our package insert are frequency plots of this type, and this is for pre-menopausal women. And what it shows is the frequency of disease, either cancer or benign disease, as a function of the cutoff, the ROMA value that you choose. And the reason we've included is that we believe that there may be some clinicians that have different -- that would like to use different thresholds. We selected cut points of 13 percent, 27 percent.

We selected them for very good reasons, and we've talked about that extensively today. But there may be clinicians that have different risk thresholds, sometimes lower, or, in some cases, higher, depending on their training, depending on their background, depending on their comfort level. So they can choose. Based on these frequency plots, they can quite readily choose cut points that they feel fits their individual practice most appropriately.

So they can slide the cut point lower if they have a higher tolerance for cancers. They can slide the cut point higher if they have a lower tolerance for cancers in their practice. So that's how we will present the data. So they'll get all of the raw data, the probabilities, and then they have the ability to adjust the cutoff as they feel is appropriate for them.

DR. NETTO: And that's based on the pivotal?

DR. ALLARD: Pardon?

DR. NETTO: That's based on the pivotal population?

DR. ALLARD: Yes, it is, correct.

DR. NETTO: These cutoffs?

DR. ALLARD: That is based on the data from our pivotal trial, correct.

DR. JASON: And that would be specified --

DR. BERRY: But that's cumulative, that's cumulative. That's not someone has a 70 percent Predictive Probability that 70 percent of those who do, you know, in the neighborhood of 70 percent actually have invasive cancer. It doesn't say that at all. That's cumulative.

DR. ALLARD: It is cumulative.

DR. BERRY: So it's not the right picture.

DR. CHAN: Also, we have not seen this data. Okay. We have not seen what he's presenting. And, also, you know, when you are -- when we're clearing this test, we are not really clearing the CA-125 and a HE4 and the ROMA all separately. So I want you to remember that.

DR. ALLARD: We have submitted this --

DR. NETTO: Say that again?

DR. ALLARD: -- to the Agency in our package insert.

DR. NETTO: Would that affect the mentioning of the lab report this way listing two --

DR. CHAN: Yes.

DR. NETTO: -- tests and then a formula?

DR. CHAN: They are going to present this way, but just bear in mind, CA-125 and HE4 and ROMA are not all cleared separately, okay --

DR. NETTO: But would, then, the FDA have concerns about --

DR. CHAN: -- but just -- the ROMA --

DR. NETTO: -- presenting this and a lab test --

DR. CHAN: Yes. We have to have more discussion with the Sponsor about how this should be presented in the data, in the report.

DR. NETTO: All right.

DR. ALLARD: So we're just addressing the mathematical formula?

DR. JASON: The ROMA test.

DR. CHAN: Well --

DR. BERRY: So you do HE4, you do CA-125, you get these two numbers --

DR. CHAN: And they are supposed to put into --

DR. BERRY: What we are addressing today is the way you put those two numbers together and can you put them together and say anything about what the implication is.

DR. CHAN: Yes.

DR. BERRY: But it's not a machine that suddenly gives you a Predictive Probability.

UNIDENTIFIED SPEAKER: It is --

DR. CHAN: They said that. That's why --

DR. NETTO: No, that's exactly what we're addressing --

UNIDENTIFIED SPEAKER: It is --

DR. NETTO: We're addressing the results of the calculation, but this is the point that was just brought up, which I mentioned is concerning, is having three numbers now because there could be some misunderstanding that the approval is for all that -- that we address the individual test or not, which we didn't. We didn't address the individual test at all.

DR. BRACCO: But it is a mathematical formula. There is no instrument or anything.

DR. BERRY: Yeah. I mean, it's not a device, you know, you --

DR. NETTO: We have no data on the individual test, and my fear is having the result for the individual test with a cutoff value, that that can also -- because what -- dangers of what was just mentioned and the clinician can really decide how they want to use the data. No, they cannot decide because when we approve that, it's based on the calculation and the data -- in the calculation in this population that we intend to restrict even further. So to open the Pandora's box and say you can just pick the HE4, I like

it this high, then may --

DR. ALLARD: No, no, no. The value that is being presented that is to be used for triage or management of women with pelvic mass is the ROMA value. There are other reasons --

DR. NETTO: So why put the others -- put the cutoffs?

DR. ALLARD: Well, there's a couple of reasons for that. One is for reimbursement purposes that they have to be shown on the lab report. Another one is that there is also a baseline value. HE4, as you know, is approved for monitoring. And the baseline value is in fact used for that purpose for serial monitoring.

MS. WOOD: Mr. Chairman, permission to speak, please?

DR. NETTO: Go ahead.

MS. WOOD: I'm Geretta Wood. I'm the director of the advisory Panel program. In an effort to bring some more control to this meeting, I'm requesting that the Panel members wait to be recognized by the Chair before they begin their comments, and I'm also asking that the FDA and the Sponsor please remain in your seats, raise your hand if you have a comment to make and wait to be recognized by the Chairman. Thank

you.

DR. NETTO: All right. Thank you. You heard it.

(Laughter.)

DR. NETTO: All right. Any other comments?

(No response.)

DR. NETTO: If no other comments, we'll take a break of 15 minutes. We'll reconvene at 3:15 -- 3:18, actually.

(Off the record.)

(On the record.)

DR. NETTO: Open Public Hearing, please. So we will have three people who requested to speak this afternoon in the Public Hearing portion.

Dr. Knapp, are you in the room? Please come forward to the podium and state your name, affiliation, and indicate your financial interests, if any, in the device being discussed today or any other medical device company. Please be reminded that due to the number of people wishing to speak, each speaker will have ten minutes on it. Thank you.

DR. KNAPP: I'm Dr. Robert Knapp. I'm the William Baker professor emeritus of Harvard Medical School and former director of gynecology and gynecologic oncology at the Brigham and Women's

Hospital and the Dana Farber Cancer Center. I'm now visiting scholar at the Wilde Medical School of Cornell University.

I'm going to speak today a little bit about -- a little background, as some of you know. I'm a co-developer of the CA-125. We first evaluated the reactivity of a monoclonal antibody with human ovarian carcinoma in 1981. And in 1983, we described the use of the CA-125 radioimmunoassay in monitoring patients with ovarian cancer who receive chemotherapy. The FDA approved a PMA for the use of CA-125 assay in ovarian cancer in 1987.

The first paper evaluating CA-125 in ovarian masses, comparison of CA-125, clinical impression, and ultrasound in ovarian masses was written by my fellow, Neil Finkler and published in *Obstetrics and Gynecology* in 1988. It is now very exciting for me to see the improvement over CA-125 in the new assay.

The risk of ovarian cancer algorithm, the ROMA, incorporates both HE4 and CA-125 in a single mathematical function and reports to the physician if the adnexal mass is low or high-risk for malignancy. This is a significant improvement over reporting just a number. The CA-125 frequently elevated in the pre-menopausal women with a benign adnexal mass, and the

HE4 is usually not elevated in a benign mass. Therefore, the HE4/CA-125 assay will be more accurate than the CA-125 assay in evaluating an adnexal mass in pre-menopausal women.

It is the physician evaluating all parameters who makes the decision as to whether the mass is possibly benign or malignant. The patient's history, including symptoms such as pain, abnormal vaginal bleeding, whether the patient is pre or post-menopausal and a family history all play an important role. The by manual and rectal vaginal examination is essential in evaluation of the mass. This will determine whether the mass is solid or cystic, its size, and mobility. The information from imaging by ultrasound, CT scan or MRI is also a part of the evaluation. It must be understood that the HE4/CA-125 assay is only part of the decision-making process in the evaluation of the adnexal mass.

In 1994, I wrote an article in the journal *Gynecologic Oncology* with the distinguished professor series: "Reflection on Ovarian Cancer, A 33-Year Experience." In the last paragraph, "the future," I stated that, "I am satisfied if the continued study of ovarian cancer is secure and in capable hands." The work on HE4/CA-125 enforces my belief that the future

is secure and that my goal will be achieved, a decrease in death from ovarian cancer.

The HE4/CA-125 algorithm is a significant advance that I endorse wholeheartedly. The FDA would contribute positively and significantly towards women's health by clearing the ROMA assay. Thank you.

DR. NETTO: Thank you very much, Dr. Knapp, thank you. Thank you, Dr. Knapp. It's an honor.

The next speaker is Ms. Tenenbaum from the Ovarian Cancer National Alliance.

MS. TENENBAUM: Hi, good afternoon. My name is Cara Tenenbaum. I'm with the Ovarian Cancer National Alliance. I first want to thank all of you for your time and your attention to this matter. You all seem very passionate, and as a patient advocate, I take that role very seriously and I appreciate your attention as well.

These comments are submitted on behalf of the Ovarian Cancer National Alliance. For 11 years, the Alliance has worked to increase awareness of ovarian cancer and has advocated for federal resources to support research that would lead to more effective diagnostic tools and treatment. The Alliance is a national organization representing more than 180,000 ovarian cancer survivors.

In addition to the individual donations from the survivor and family community, we receive some funding from pharmaceutical and biotechnology companies, including Fujirebio. We have a strict policy that fundraising efforts do not affect our policy work, including my presence here today. The Ovarian Cancer National Alliance supports evidence-based medicine and does not endorse any specific device, drug, or therapy for ovarian cancer.

The Ovarian Cancer National Alliance conducted a survey in 2007, the results of which I'll be referring to. Results generally showed, however, that women with ovarian cancer, one, tend to see multiple doctors before being accurately diagnosed as having ovarian cancer; two, are diagnosed at late stages of the disease; three, have their symptoms confused with symptoms of other diseases and conditions; and, four, are generally unaware of genetic tests or other risk factors that could help detect the propensity to develop ovarian cancer. In my presentation today, I will refer to some of these results.

I'm not going to repeat the grim statistics that we've already heard today about ovarian cancer and that show the need for an accurate and reliable early

detection, risk stratification or other diagnostic tools. But I will remind you that the majority of women with ovarian cancer continue to be diagnosed in Stages 3 or 4 when survival rates are low.

One key reason is that a valid and reliable early detection test does not exist for ovarian cancer. The CA-125, as you've heard numerous times today, is not a screening test, and it's not approved as an early detection test. Respondents to our survey share personal stories of delays that prevented an early diagnosis. One told us about her sister's story, which I'm going to -- very short:

> "My sister was 43 when she was diagnosed with ovarian cancer. She had been going to the doctor for almost a year with symptoms of ovarian cancer before she was diagnosed. She was told she had GI problems or she was pre-menopausal. At one point, a doctor told her he couldn't find anything wrong with her. She said she was in extreme pain. What should she do? He said if it gets really bad, go to the emergency room. She went home and went to the emergency room that night. They did several tests and found out she was full of fluid. Later that week, we found out

she was in Stage 3 of ovarian cancer."

Early and comprehensive testing for ovarian cancer remains a critical need. Our major survey results show, one, most women are unaware of ovarian cancer symptoms. Almost 90 percent of respondents to the survey, most of them being survivors, were unaware of the symptoms. Yet, in retrospect, more than 80 percent of them had exhibited some of these symptoms. The inability of both women and their healthcare providers to recognize these symptoms as being indicative of ovarian cancer means a test, which we have today like the CA-125, ultrasound, were not used.

Most women first see a general practitioner. They don't see a gynecologic oncologist. One woman said:

> "I'm 48 years old and I was diagnosed with ovarian cancer six months ago. I had not been feeling well for over a year and had been to several doctors, who had dismissed the symptoms as being early pre-menopausal, fibroids, benign ovarian cysts, stress, appendix, constipation, depression." My periods had become very heavy and painful, and then I started bleeding in between periods. At that time, one of the doctors

recommended an endometrial ablation, which I had done, and he noticed that my right ovary did not look good but did nothing about it. I continued feeling not well, having lower back pain, pain on my right side, feeling bloated, gaining weight, and feeling sick. About seven months later, I made an appointment with another gynecologist. She did an ultrasound and did not like what she saw. She sent me to get a CA-125. I had no idea what that was until that day. When I found out what I was being tested for, I was scared. I was stressed out and scared for three days before I found out the results, that I had ovarian cancer. My daughter, who is 14 years old, was with me the day my doctor told me. My whole world came apart."

Women are largely unaware of gynecologic oncologists. Our survey shows that about 50 percent of respondents did not know about the specialty and about 40 percent of them said that their doctors who evaluated their symptoms did not refer them to gynecologic oncologists.

Dr. Berry, I think you said something about we should just flip a coin, and if only 50 percent of

patients are seeing a gynecologic oncologist -- I'm sure you didn't mean to be crass or flip, but that's about the care they're getting. Correct diagnosis occurs only slightly more often than incorrect diagnosis. About 41 percent of the women who responded to our survey were treated for other conditions, including the ones I've mentioned, acid reflux, endometriosis, pre-menopause, nerves, stress, irritable bowel syndrome, gall bladder, allergies.

The results of the survey show that women and their healthcare providers do not always consider the exhibited symptoms as signs of ovarian cancer. We know the importance of referral to a GYN oncologist, and any support for referral to them will aid patients in survival.

The improvement in the accuracy of any risk stratification device could encourage testing among general practitioners who may be reluctant right now to use methods that have limited accuracy. This, in turn, could lead to women being diagnosed earlier and increase survival. I want to make the point that a reliable test will be used by more front-line doctors. Currently, they don't use the CA-125 because it's not hugely reliable.

And I have a couple questions to you as you

go into your discussion. I'd like you to think about the risk to women for using this test that's been proposed and how that compares to the risk of not using the test. If this test is not approved, what other tools do women and their doctors have? And recognizing that the Sponsors are not asking for this, but if the test is only approved for use by GYN oncologist, not front-line doctors, how does that help women? And what would the burden be on women to wait for this or other tests to be studied among front-line doctors, given the incidence of ovarian cancer and the time it might take to complete those studies.

Thank you again for your time and attention.

DR. NETTO: Thank you very much. Next is Dr. David Fishman from NYU Cancer Institute.

DR. FISHMAN: Well, this should be entertaining since I'm never politically correct, and I'm not going to start. My name is Dr. David A. Fishman. I'm the director of gynecologic oncology at New York University School of Medicine. And as some of you know I have a long-standing interest in early detection and actually use our tax dollars from the National Cancer Institute to perform a lot of our research on ovarian cancer. My travel was covered by the Sponsor today. And I want to thank you for the

opportunity to come and see old friends and hopefully make new ones.

My hat today I'm going to wear is as a gynecologic oncologist who actually takes care of patients. And the problem that we have, as we've seen today, is that we have no tools that help us detect early-stage disease, and there are no tools that are available. And as we've heard today, this is unacceptable because our success in curing women with ovarian cancer is the same as it was in 1960. I'm talking cure, not three-year survival or five-year survival.

Any tool that would help us identify women with ovarian cancer and have them referred to and be treated by a gynecologic oncologist has been proven to save lives, decrease morbidity, pain and suffering, and any tool that can have value is important to be brought into clinical use as long as it meets the metrics you decide because I as a clinician and those of you who take care of patients want to have tools that we can say we believe in. So we hear you, and I think your questions have been outstanding.

I want to explain what a gynecologic oncologist is because, other than Ralph, I think there is only one of you there who is a gynecologic

oncologist. We are the only board-certified physicians in the world, and the United States is the only country that has board-certified clinicians who are trained experts in dealing with a treatment and diagnosis of women with gynecologic malignancies. Only the United States has this as a board-certified specialty. There might be 1,000 of us in the United States. This is a tremendous honor to take care of these women. We do not take this lightly.

Women's healthcare is compromised, as is proven by multiple articles when they're operated on by non-gynecologic oncologists even if it's something simple as spilling a capsule, an ovarian mass cancer that's confined to the ovary, if it's ruptured and there is no other cancer found, that person just went from not needing any further therapy to buying at least three to six months of chemotherapy. Think about the cost of quality of life and societal costs that incurs. So optimizing patient triage is a critical step to saving women's lives.

The thing I've heard today is why refer anybody back? You're right. Gynecologic oncologists are the best skilled pelvic surgeons in obstetrics and gynecology. I won't say we're the best vaginal surgeons. You guys probably are. But the bottom line

is if we took every patient that came to us, there has to be a fairness here.

If I have a patient that I think is benign, and I am a practicing doctor who does do a lot of surgery, I'll send them back to the referring doctor, saying, "I don't know whether she has cancer, but I've had the discussion with her. So preoperative consultation, discussion, meeting with the patient, not an intraoperative disaster parachuting in, but talking to the patients if this is cancer and if it's not cancer, talking with the doctor, informed consent, decreasing anxiety. And if the patient does have cancer, I make sure I'm available surgically to help my colleague out. So we can optimize patient care.

What else is missed? If patients aren't optimally debulked at time of surgery, then they're probably not going to have an intraperitoneal Port-a-Cath placed. Our standard of care has changed. Now, whether you -- intraperitoneal therapy or not, it doesn't matter. We can optimize patient care in one operation. If there is a delay, that's fine, as long as the patient is referred. But when the delay is 16, 17, 18 weeks, that's unacceptable.

You talk today about intraoperative frozen analysis. Well, with all due respect to Brown, most of

us have a 50 percent accuracy rate for intraoperative frozen analysis. And certain tumors, mucinous especially, are very difficult to determine. LMPs can be wrong, and a lot of us will stage these patients because invasive implants is cancer. It's not benign disease, and we can discuss it with Bob Kerman later.

The bottom line is that we want to optimize patient care. We have no good tools. Any tool that will help us improve patient care, even if it's something as simple as getting them referred to a gynecologic oncologist, will save lives. Maybe I'm beating that over the head, but I think this is important to hear. As a clinician who takes care of patients, any tool that we have that we can have faith and confidence in is important to bring to the table. I do not own stock in this company, nor am I buying stock in this company.

I'd like to thank you all for at least allowing us who take care of patients to talk to you. And as a gynecologic oncologist, I'd like to let you know that those of us in this specialty and all of you who are healthcare providers take great pride in optimizing our patient care. We believe this is a tool that will help. I hope you will as well. Thank you.

DR. NETTO: Thank you very much, Dr. Fishman.

At this point, we will proceed to the FDA and Sponsor summation, if any. Is there any further comment or clarification from the FDA?

(No response.)

DR. NETTO: All right. Thank you. Is there any further comment or clarification from the Sponsor?

DR. ALLARD: Yes, thank you very much, Mr. Chairman.

DR. NETTO: Ten minutes, please.

DR. ALLARD: Very good. We will do that. I will introduce Dr. Moore for one final time. I just want to make the statement that Fujirebio remains committed to bringing better diagnostics to bear on this awful disease. This is the mission of the company, after all, and they believe in it. And they will continue to invest in this area because of their commitment, and they look forward to working with you and with the FDA to improve the labeling of the product to the extent that that's necessary.

I'd like to introduce Dr. Moore, who will deliver a brief summation.

DR. NETTO: Thank you. Dr. Moore?

DR. MOORE: It's truly been amazing that CA-125 was discovered over 30 years ago and we're finally getting tumor markers that are going to help us improve

the care of ovarian cancer. As gynecological oncologists, we are dedicated to decreasing the suffering that these patients have to undergo. The board-certified gynecological oncologists, we're committed to improving women's healthcare by increasing survival and decreasing the pain and suffering associated with gynecological cancers. We are the only board-certified physicians, as you have heard, and physicians that are trained to surgically and medically manage women with ovarian cancer.

The literature clearly indicates, as we've shown today, the survival is improved for those women whose initial surgical care is managed by a gynecological oncologist. Unfortunately today, just as in 1975, the majority of women with ovarian cancers are not referred to gynecological oncologists when they present to their primary physician with suspicious adnexal masses. And we've heard that from our patients and our patients' advocates today.

Today, the vast majority of women with epithelial ovarian cancer continue to be diagnosed with advance stage disease and have dismal prognoses. We need to be better at taking care of and diagnosing these patients. Therefore, we've got to ask ourselves, we have to ask ourselves how can we do better. We have

to ask that question to us in order to take care of our patients, and we have to ask what tools can we use today to save lives of our loved ones. This is a very serious disease, and we need every little tool that we can use to help improve the survival for this deadly cancer.

ROMA is a novel objective ovarian cancer risk assessment tool and the only algorithm and the best test available to distinguish benign from malignant masses. It is imperative that the Panel understands that ROMA is intended to be used only in the population of women who have a pelvic mass and are going to have surgery. It's not intended to be used as a diagnostic tool, nor is it intended to be used as whether women will undergo surgery or not undergo surgery. Rather, ROMA will allow us to more accurately identify those women with a pelvic mass at risk for ovarian cancer.

Also, remember, there is currently no FDA-approved or cleared objective test for stratifying risk of ovarian cancer in women with a pelvic mass scheduled for surgery. CA-125 is not FDA-approved for diagnosis, screening or risk assessment of ovarian cancer. However, the pilot studies were appropriately powered, as we've talked about, and found to have a significant additive effect to HE4 and CA-125. The pivotal study

was not designed or powered to detect the difference between CA-125 and ROMA. It was appropriately powered and designed to detect ovarian cancer in women with a pelvic mass.

The ultimate benefit of ROMA is to improve women's healthcare. The appropriate care of women with a pelvic mass utilizes multiple clinical tools, including detailed personal and family histories, physical examinations, diagnostic imaging, and, now, ROMA should be one of those tools included.

In the intended use population, ROMA will help us in preoperative planning and patient counseling and can influence surgical approaches. Based on the data, ROMA will allow us to help optimize women's healthcare and save lives. Thank you.

DR. NETTO: Thank you, Dr. Moore. At this point, I would like Dr. Chan just to make a comment about the logistics and the upcoming questions.

DR. CHAN: I'd like the Panel to keep in mind that FDA do not regulate medical practice, and we will really try very hard to build a firewall in the labeling to keep off-label use, you know, as much as we could. And, also, in your deliberation/discussion of the questions we're going to pose in a few minutes, to keep in mind this is limited to the intended use that's

specified for this device. Thank you.

DR. NETTO: Thank you. Which bring us to the FDA questions. At this time, we will focus our discussion on the FDA questions. The FDA -- interviewer will now read the questions. Dr. Reeves?

DR. REEVES: Actually, what is the Panel's preference with regard to this? Should I just display the questions? Do you want me to read the questions out loud? I will do as the Panel desires.

DR. NETTO: We have the questions in front of us. All right. So what's the decision? Would you like Dr. Reeves to read it or -- so question number 1.

DR. REEVES: My apologies. I hit the wrong button. Okay. What's your desire? Do you want me to read the questions out loud?

DR. NETTO: Go ahead and read it, yeah. Go ahead and read it.

DR. REEVES: Okay. Fine.

Question 1: The proposed intended use population is "pre-menopausal and post-menopausal women presenting with an adnexal mass who have already been referred to an oncologic specialist and are scheduled for surgery." Bearing in mind the likelihood that different populations vary in their disease spectrum and clinical performance by the test:

(a) Does the population accrued to the pivotal study adequately match the population and indications described in the Sponsor's proposed intended use?

(b) Is the proposed intended use sufficiently clear and appropriately crafted to prevent ill-advised use of the test beyond its stated indications?

(c) If "no," how can this be remedied in labeling or through obtaining additional data?

DR. NETTO: Thank you. Any discussion from the Panel?

DR. BERRY: I think the answers are yes.

DR. NETTO: To which one?

DR. BERRY: (a) and (b).

DR. NETTO: Does the population accrued to the pivotal study adequately match the population of indication? Yes.

DR. BERRY: (b), I'm not sure; (b) there may be some statement that there have been no studies in the actual clinical practice of -- in your general practitioner use of this procedure, but it should be done in the context of a referral clinic.

DR. NETTO: But that's not what the intent to use is. It's not the general practitioner. So they intend to use -- let me remind you exactly how --

DR. BERRY: But I thought it said the pre-menopausal/post-menopausal women presenting with adnexal mass who have already been referred to an oncologic specialist and are scheduled for surgery.

DR. NETTO: Correct.

DR. BERRY: So I'm saying, specifically, it could say in the label, this is not for use --

DR. NETTO: Exactly --

DR. BERRY: -- of, you know, in the ordinary clinic. It hasn't been shown to be beneficial.

DR. NETTO: So you feel it would -- the intent to use will benefit from adding a negative sentence --

DR. BERRY: Yes.

DR. NETTO: -- to prevent this concern that several members of the Panel felt?

DR. BERRY: Yes.

DR. NETTO: Go ahead, Dr. Bracco.

DR. BRACCO: I just want to comment that I think the intended use is confusing enough, and I think we should take advantage of, actually, 21 C.F.R. 809, which I know the FDA is very familiar with. Those are the labeling requirements for in vitro diagnostic devices which require adequate limitations and warnings to be presented in the labeling. And, Dr. Chan, to

your point, it is not FDA's purview to regulate medical practice, just to provide the physicians with the proper information so that they can make the right decisions.

So I think the intended use, as I said earlier, should either be set back to its original intended use with some very strong limitations and warnings in the labeling, or kept as is and also include the limitations and warnings to make sure that it's very clear to the medical community in which populations this device was studied and we have the clinical data for.

DR. NETTO: All right.

MS. LONDON: I have a comment regarding Question 1(c). Referring to the insert page on Architect Systems, I think it would be helpful if under United States they have 1-800-4ABBOTT, but it doesn't express time of day, 24/7, Monday through Friday, 8 to 5. Medicine goes around the clock, and it would be very frustrating to be a clinician or a tech or a healthcare person calling the Pacific Coast and not being able to find out an answer. And so, specifically, how can this be remedied in labeling? That would just be a very simple addition to the label.

DR. NETTO: Thank you. Which brings an

issue. The labels that are included in the package are toward the two test components, is that --

DR. CHAN: The labeling is actually for the laboratory. It's not for the physician to call Abbott, you know --

MS. LONDON: Okay.

DR. CHAN: The physician is not going to perform the CA-125 test. And --

MS. LONDON: Who would be calling the --

DR. CHAN: It's the laboratory, like --

MS. LONDON: Well, it would help them to know the hours as well, the hours that the phone number will be answered. Is it 24/7? Will you get an answering service --

DR. CHAN: Usually, you can access Abbott all the time.

MS. LONDON: Okay.

DR. CHAN: If you have a technical issue --

MS. LONDON: Okay.

DR. CHAN: -- you know, they will respond back to you. And so I think the labeling for the CA-125 for the Abbott should be okay.

MS. LONDON: Is sufficient?

DR. CHAN: Yeah, is a normal -- normally, that's how the labeling is done.

MS. LONDON: Okay.

DR. CHAN: Thank you.

DR. NETTO: But introducing modifications to the intention of use, if this Panel has a suggestion for introducing, from what I'm gathering, modification to intention of use, if the feeling was that it's not clear and appropriately crafted, addressing number 1(b), question 1(b), where would these additional suggestions be included? Not in the laboratory packaging, right?

DR. CHAN: No, no, it will be in the labeling of the test. And it will, you know, of course it will be sent to the laboratory, and the laboratory, when they give a report to the physician, should include the limitations in their report. So we have to discuss further about how to handle it, but we would prefer as stated what the -- how we recommend the intended and indication for use to be for this stage. But we can add additional limitations after that.

DR. NETTO: Okay.

DR. CHAN: Thank you.

DR. NETTO: Go ahead.

MS. HOLLAND: I just want to say I think the ROMA is very valuable as a tool, so I don't want anybody to misconstrue what I've said to think that I

don't think it has value because I really do, but I also have an issue with the labeling. I think, you know, that we've talked about it before, but I want to reiterate. At a time when it's understood the value of having surgery done by the specialist, the labeling seems to turn that around and want to send people back away from the specialist, and my opinion is that if there is any suspicion of malignancy that we need to be seeing a specialist. So that's my problem. How to solve that problem in labeling I'm not sure. I think other people might be able to solve that better. Thank you.

DR. NETTO: Dr. Ozols?

DR. OZOLS: Yeah, a couple of things. The labeling is somewhat misleading. First of all, who is an oncologic specialist? People are going to argue, are you just meaning gynecologic oncologists? How about a surgical oncologist who does -- pelvic surgeon or a GI surgeon, but he just does oncology, is he an oncologic specialist?

Scheduled for surgery is very vague. I mean, surgery is scheduled often, you know, a week before the operation, but all sorts of tests are being done the mean time. Scheduled for surgery, I'm not -- scheduled, what does that mean?

Second, you know, I think (a) is probably okay with those caveats, but (b), I think (b) is probably no because, as we talked about, that it's going to be used in an ill-advised manner. And the answer to (c) is how we can do it. I think you need to -- how you can remedy this, I think you can remedy this by doing a trial in the patients who are really going to be used in the sense that this should be looked at in a community situation in a randomized trial to see if it's really beneficial because it's basically going to be in the reverse process, ultimately, to go to refer patients from the community to the specialist, whoever that is.

DR. NETTO: Dr. Berry?

DR. BERRY: I just want to comment on that. Unfortunately, we can't remedy that in the label. I mean, I agree that a study like that would be appropriate, but we can't put it in the label --

DR. OZOLS: Well, I'm talking about additional --

DR. NETTO: You can suggest additional data because that's question (c). If your answer to (b) is no, how can the -- and correct me if I'm wrong -- how can this be remedied in labeling or through obtaining additional data --

DR. BERRY: Oh, okay, all right.

DR. NETTO: So you can suggest --

DR. BERRY: Yeah, yeah, yeah.

DR. NETTO: -- if part of the remedy is --

DR. BERRY: Not in labeling but in additional --

DR. NETTO: -- obtaining additional data, is that correct? Does anybody else share the feeling of Dr. Ozols?

DR. FREEDMAN: I have the same concern because when we're asked to comment on whether it can be crafted to prevent ill-advised use of the test, this becomes very difficult since we're not allowed to put certain things in there. On the other hand, clearly, if there is a potential here for abuse and misuse and that could impact on the safety of patients if it were not properly used. And I think one of the -- with regard to (c), I know that there is additional data that the Sponsors generated at least in 80 percent of the patients that they didn't complete and didn't present to us on the correlations with the radiologic and other studies, it would at least be interesting to look at that. And since the study was done, it was a secondary objective, patients participated in the experiment to provide data for the primary and

secondary endpoints, I think it's probably incumbent on us to look at it at least at the secondary endpoint.

DR. NETTO: Dr. Julian?

DR. JULIAN: I agree. I think (a) is yes. (b) is no.

DR. NETTO: And the remedy?

DR. JULIAN: All I can say is it was a great honor to hear from Dr. Knapp to be speaking about CA-125 and it being introduced in 1981. And I remember in '88 through '92, when every patient who came in for an annual exam wanted a CA-125 as part of the diagnostic panel. And I can remember all of the ovaries we took out of people who had moderately or mildly or just marginally elevated CA-125 during that period.

So I don't think there is any way you could keep this test out of the hands of the community. And once it's in the hands of the community, if a great contribution like CA-125 is not being handled correctly 27 years later, I think that something needs to be done to get this into the community, see how it works there because you know that's where it's going to end up anyway.

DR. NETTO: So are you suggesting additional data --

DR. JULIAN: I think you need to test this --

DR. NETTO: -- within the community similar to the other --

DR. JULIAN: I have nothing against the test per se, but the question as stated here, that's what I think.

DR. NETTO: Go ahead.

DR. FUNKHOUSER: I'd say I agree yes to (a) and no to B. I think the current stated indications are too narrow. I think that triage from GYN/ONC back to local practice -- direction in the wrong way. I think the more common the usefulness of this test is in triage in patients from a local GYN practice to specialist care in a tertiary care center. And for that reason, trial data should be accumulated addressing that particular intended use before the FDA puts -- on this test.

DR. NETTO: Although on the other hand, our job is to evaluate according to intent of use. But if the feeling is that intent of use is confusing and doesn't clearly and appropriate crafted, which could lead to ill-advised use, then I understand the comments. Dr. Lichtor?

DR. LICHTOR: I guess I'm still puzzled about who should be ordering this test, so this question sort of acts like only a oncologic specialist should be

ordering it, and then you're giving the restriction not only does a patient have to come to an oncologist, but has to be scheduled for surgery. To me, the scheduling for surgery should be taken out. I'm a surgeon. I mean, that could be -- it's so vague, and I don't even know what that really means, and I think that's just opening up doors you don't want to open up. You can just decide you want a test that only a oncologic specialist should order or is it a test that any family practice or obstetrician could order. I think that's, to me, the issue. And then I could answer the questions. But the way this is written, I don't even feel I can answer the questions.

DR. NETTO: So you're -- but it sounds like your answer to (b) would be no or yes?

DR. LICHTOR: My answer to (b) would be no.

DR. NETTO: And as far as the remedy, you don't have a suggestion?

DR. LICHTOR: I'm sorry, what?

DR. NETTO: And as far as the remedy, to (c), your answer to (c)?

DR. LICHTOR: Well, I mean, I think it has to be reworded, which is -- I mean, I would take out scheduled for surgery, and I think you have to decide is this something that an oncologic specialist only can

order or is this something that any oncologist could order? To me, that's the issue. And then I could answer the other questions because this is --

DR. NETTO: Okay. But we're kind of restricted by the fact that the pivotal study was done in an oncologic --

DR. LICHTOR: I understand that. No, I've heard all this discussion. I understand it. But it's still --

DR. NETTO: Correct. Correct.

DR. LICHTOR: But it's still begging the question as to it seems to me once you approve this test, anybody could probably order it. That's the way I look at it, and so I think you've got to assume that that's going to happen and address that issue. Say we think it only should be ordered by oncologic specialists, and I'm on the fence on that or -- because you don't really have the data. Or you could write only oncologic specialists until more data is available, or something like that.

DR. NETTO: Okay.

DR. LICHTOR: I mean, to me, it's got to be reworded.

DR. NETTO: All right. Anybody else?

DR. BRACCO: Can I just make one

additional --

DR. NETTO: Sure, go ahead.

DR. BRACCO: There are devices that come to mind. One in particular is a brachytherapy device for breast cancer following a lumpectomy. And those devices have been out there for years and successfully used without any clinical data to show how they fare against whole breast radiation. But all of those devices in the public domain all carry a warning, a very strong warning, that they haven't been adequately studied against whole breast radiation. So there are devices out there that fall under a similar circumstance where labeling does seem to be doing its job adequately. And --

DR. NETTO: So you're suggesting -- so the suggestion would be to add wording to say, to clearly state that it was not studied in the setting of primary care --

DR. BRACCO: Right. So to your point about needing an additional study, that can clearly be stated in the labeling, but here is what we have right now, and then it's up to the medical community to decide how to use that. But they have the adequate warnings in front of them to make that decision.

DR. NETTO: Thank you. Dr. Jason?

DR. JASON: Could I have just two things? Do you need me -- or just what I want to add?

DR. NETTO: No, your answer to this question. Well, what do you want to add --

DR. JASON: Okay. In terms of something to add, I think in terms of what the material says the intent is, it actually doesn't match what we've heard today. For instance, Dr. Moore now is saying he would not use it to refer someone back. So I think there's very definitely a lack of clarity in terms of what the intended use is even in terms of our discussion today. So I'd have to say in terms of Item Number --

DR. NETTO: 1(b)?

DR. JASON: -- (b), it is not clear and maybe needs to even be rethought-out. And, you know, I am not a gynecologist or oncologist, but I could put on a hat of education. Once this thing is finalized, it would be good to test it against this charted population and see if it's clear to them. But it's definitely at the end of today less clear to me than it was at the beginning of the day.

And in terms of how to remedy it, and I defer to the people who work in this area, clearly, it is not quite right for its stated intended population, and it may need to be -- may need to involve further work if

other people are going to read it and use it and then misunderstand it.

DR. NETTO: Go ahead, Dr. Berry.

DR. BERRY: So I want to comment on Dr. Lichtor's comment and Dr. Ozols about scheduled for surgery and the suggestion that it be dropped. I don't want to drop it. I think it's essential to be in there despite it being ambiguous. I mean, we don't know what it means, but that's what the study was, was all patients who were scheduled for surgery. And so somebody looks at this and says, gee, scheduled for -- what does that mean, at least he or she is thinking about it, and it puts kind of a damper on the kiddie bar to the door attitude.

DR. NETTO: Right. So if nobody else has a comment, we are supposed to summarize this to answer back to the FDA, so anybody else?

(No response.)

DR. NETTO: So as far as suggesting, what I'm hearing is that it seems to be a consensus that as it's currently intended, it's not sufficiently clear and to prevent especially ill-advised use, which, again, we have no power in enforcing that ill-advised, but we can build in some parameters to protect from that.

So it's a feeling that the sentence,

"Subjects categorized as low-risk may have surgical intervention performed by a non-oncology specialist should -- does anybody feel that striking this out with -- because it seems like we are opening the path for that if that's the concern. At least we shouldn't be suggestive of that unless you guys feel otherwise.

UNIDENTIFIED SPEAKER: Question 2(a)?

DR. NETTO: No, that's in the same question. I'm going back to the intention to use statement. And one of the sentences there is, "Subjects categorized as low-risk of cancer using the ROMA value may have surgical intervention performed by a non-oncology specialist." So if --

UNIDENTIFIED SPEAKER: That comes to 2(a) again.

DR. NETTO: Yeah, it comes again? Yeah. So is the general feeling that this may be a little suggestive that -- for that reverse referral issue that we talked about?

DR. JASON: Well, Dr. Moore says he's not going to use it that way, so I don't know that -- you know, you had said you would not refer them back. You would use it make decisions on how to do your surgery and what kind of approach.

DR. FREEDMAN: I wouldn't emphasize the

individual. I would emphasize the field of oncology, in other words, in an oncology setting. I think then it doesn't sort of deal with, you know, the personalities and those issues because it was done in an oncology setting. And, I mean, that's appropriate.

DR. OZOLS: But we have no data on the use of this test when -- if it was, you know, used and those patients were operated on by a non-oncologic surgeon because all these patients in this pivotal trial were operated on by an oncologic surgeon. So we don't have any data to suggest what happened if they would be referred back to a non --

DR. NETTO: So it would seem to me it would not be appropriate to put that --

DR. OZOLS: Yeah, we don't have --

DR. NETTO: -- in the insert that based on that they cannot -- they can be sent back because none of these patients were sent back.

DR. OZOLS: Right. We have not a shred of information.

DR. NETTO: So would you recommend that this sentence be removed from the intention to use, and how about the suggestion that -- to add a sentence regarding more restriction in term of until data is acquired in term of community performance? How would

you craft that?

DR. BRACCO: That actually wouldn't be a sentence in the intended use. It would be a sentence in the limitations or warning section of the labeling.

DR. NETTO: Okay. So that's something that needs to be -- that can be considered. All right. That's our answer to the first question.

DR. FREEDMAN: I'm sorry. Can you just tell me again? So you're going to take out the portion that says who have already been referred to an oncologic specialist? Which part --

DR. NETTO: My feeling, yeah, my feeling that "and are scheduled for surgery" --

DR. FREEDMAN: We're taking out scheduled for surgery?

DR. NETTO: It seems like different people have different opinion. What's the general consensus on that?

DR. JASON: What is the question? What are you specifically asking?

DR. NETTO: About whether the sentence about referred to and scheduled for surgery, whether the scheduled for surgery portion needs to be specified, left specified as is or not? Go ahead.

DR. BRACCO: I just want to go back. It's in

the Panel pack somewhere, but the original labeling says pre-menopausal/post-menopausal women presenting with an adnexal mass who are candidates for surgical intervention period.

DR. FREEDMAN: Candidates.

DR. BRACCO: With all the labeling restrictions around that, I think that's clearer than, like I said earlier, something the FDA I believe put in to cover some of the limitations in the clinical -- in the cohort that was studied, which actually made the intended use, in my opinion, more confusing.

DR. NETTO: But there is no mention of oncology setting, correct, which is --

DR. BRACCO: Well, we can add that. I mean --

DR. NETTO: I think that needs to be added --

DR. FREEDMAN: Candidates for surgery --

DR. NETTO: Whether it's candidate for -- yeah, in an oncologic setting.

DR. JASON: Now, you're referring to something not in our packet, is that correct?

DR. NETTO: So rather than schedule for --

DR. JASON: Because my packet.

MS. HOLLAND: It's in a different place. I don't know where it is either but --

DR. JASON: Because Page 1 of the HE4 reads --

DR. NETTO: Right.

DR. JASON: That is for those who have already been referred to an oncologic specialist and are scheduled for surgery.

MS. HOLLAND: Right, but what he's saying is it may be better to use the other terminology.

DR. JASON: That's what I'm saying --

DR. BRACCO: It's on Page 10 --

DR. JASON: He's going back to something else.

DR. NETTO: Excuse me just one second.

UNIDENTIFIED SPEAKER: Page 10.

DR. NETTO: So let me clarify --

MS. HOLLAND: So we're talking about two different issues here --

DR. NETTO: Excuse me. Let me just -- in the briefing document, in Chapter 2, there is a paragraph about the modified version of what the FDA suggested the intention to use modification should be. And that's what we're referring to and trying to modify that. So rather than putting scheduled for surgery as is, who are candidate for surgery, I think that would make everybody --

UNIDENTIFIED SPEAKER: Surgical candidates.

DR. NETTO: That's fine, yeah. But in an oncologic setting --

DR. FREEDMAN: In an oncologic setting.

DR. NETTO: Keep the oncologic setting there and drop the sentence about the low-risk patient because it seems a little suggestive to go back to -- right. And my general feeling is we should have a sentence under the limitation, like we discussed, about this has not been tested in a population base and this should not be used in that setting as a limitation. Everybody agree on that?

DR. REEVES: I'm sorry. Could you say that again? I didn't hear you very well.

DR. NETTO: Sorry?

DR. REEVES: I did not hear that very well. Could you speak --

DR. NETTO: So as far as the limitation, the added limitation should be a mention, and whatever the FDA feel appropriate, that this has not been tested in the general population. I think it should come with a positive sentence about that because it's not mentioned. It's just emphasizing that you can use it in the oncology setting. I think we should have a sentence saying that -- suggestion of the Panel would

be to have a sentence saying this has not been used, tested in a primary setting, in a population-based setting, and has only been tested in an oncology setting and should not be used in a primary population setting.

DR. BRACCO: But not in the intended use statement. That extra sentence --

DR. NETTO: In the limitations --

DR. BRACCO: Right.

DR. NETTO: Yeah. Would that be okay in the --

MS. HOLLAND: So it's actually three different changes or two changes, or two changes and one addition --

DR. REEVES: In the limitations section, saying that is has not been tested in the --

DR. NETTO: In the population-based --

DR. REEVES: In the general gynecologic population.

DR. NETTO: Correct. And it's not intended for use in that setting.

DR. REEVES: Okay.

DR. NETTO: Because it has not been tested in that setting. And as far as the intention to use is just to change the scheduled for surgery to --

MS. HOLLAND: Right, so there is one change, there's one omission --

DR. NETTO: Correct.

MS. HOLLAND: -- of a sentence, and then there's --

DR. NETTO: Limitation --

MS. HOLLAND: -- an addition to the warnings.

DR. NETTO: Correct.

MS. HOLLAND: So three different things we're talking about. Is that clearer?

DR. NETTO: Is that clear?

DR. REEVES: The third item I'm not clear about.

MS. HOLLAND: The Item 1 was to change the language -- I'm sorry.

DR. NETTO: So the first --

MS. HOLLAND: Is it okay if I --

DR. NETTO: So I'll summarize. So the first suggestion was the scheduled for surgery language to be changed and replaced by who are candidate for surgery.

DR. REEVES: Right, I understand that.

DR. NETTO: The second suggestion is the sentence immediately after that, "Subjects categorized as low-risk for cancer using the ROMA value may have surgical intervention performed by non-oncologist," to

be deleted because it's a little suggestive that you can send them back.

And the third suggestion is according to what the FDA feel is either to insert a sentence there indicating the limitation that this has not been tested in the general population setting and is not intended for use in that setting. So either to add it as --

DR. REEVES: In the actual intended use rather than in the limitations section of the label --

DR. NETTO: And that's where we need your advice in term of is it appropriate to put it under limitation or --

DR. REEVES: Fine, I understand that. Thank you.

DR. NETTO: Or in the actual -- go ahead.

DR. BRACCO: I think striking out that one sentence and not putting anything in there kind of leaves you lacking more so, in my mind, in terms of what you're going to use this device for.

DR. NETTO: I think actually that's where -- I mean, my understanding is, if we can add the sentence that I just talked about in term of not being tested in the primary setting, if that can be put there, I think it comes strengthens the point that this is only restricted -- was tested in an oncology setting. And

having the sentence there talking about that primary setting was not tested and it's not indicated for use there. It actually not only will reverse that suggestion to take them back --

DR. BRACCO: Okay.

DR. NETTO: -- but it will enhance it further.

DR. BRACCO: So where in the intended use will it say what to do with this result now that you've taken out that sentence?

DR. NETTO: It's the next sentence. The results must be interpreted in conjunction with other clinical findings and according with standard clinical management guidelines. The assay is not indicated as an aid in a decision to proceed to surgery. I think --

DR. BRACCO: So it just says to use it with other clinical results, but it doesn't say what to do with that -- this particular algorithm?

DR. NETTO: I don't think the study illustrated anything on what to do when you have that test result one way or the other. It just showed that in the pivotal population was -- seems to be prognostic. Is that an agreement? Does that summarize --

DR. OZOLS: Yeah, we need more data. We

would like to see more clinical data, but they don't have it. So we can't recommend -- data --

DR. REEVES: Okay. Is the Panel --

DR. NETTO: Okay.

DR. REEVES: -- ready to move on?

DR. NETTO: Let's move on to the next --

DR. REEVES: Okay. Question Number 2 is a rather long one:

The following were among the estimates of clinical performance characteristics yielded by the pivotal study for all evaluable patients in the study population described for Question 1 (where the total number was 504 subjects, excluding 28 cancer patients whose tumors were not epithelial ovarian cancer), and the table is presented.

(a) Are these results consistent with safe and effective use of the test in selecting low-risk women for whom surgical intervention performed by a non-oncology specialist is appropriate?

(b) If "yes," what special measures (if any) need to be in place in order to ensure safe use of the test?

(c) If "no," how can this be remedied in labeling or through obtaining additional data?

(d) For the specified intended use population

and indication, what is the clinically tolerable maximal percentage of patients who are falsely categorized as "low risk"? Said another way, what is the maximum tolerable (1-NPV)?

(e) For the specified intended use population and indication, what is the clinically tolerable maximal percentage of patients who are falsely categorized as "high risk"? Said another way, what is the maximum tolerable (1-PPV)?

DR. NETTO: Okay. Dr. Ozols?

DR. OZOLS: Well, (a) to be consistent with what we just recommended, the answer is no because we have no idea whether it's safe for these women to be operated on by a non-oncology specialist. So if this question, are these results consistent with safe and effective use of the test in selecting low-risk women, I would say the answer is, yes, if you stop the question at that point. But I don't think we have the data to say that it's safe and effective if that surgery is done by a non-oncologist.

DR. FREEDMAN: I agree.

DR. NETTO: Okay. Dr. Freedman agrees?

DR. FREEDMAN: I agree.

DR. NETTO: Dr. Berry?

DR. BERRY: I agree, but I want to comment on

the table before (a). It's very unusual to give sensitivity -- negative predictive value as summaries. It's standard to give sensitivity and specificity and, if possible, positive predictive value and negative predictive value. It's very strange to do it in the mixture that they've done it. With that in mind, if they did positive predictive value, and I think it's an appropriate thing, I don't believe the company provided positive predictive value, but the -- for broken out by pre and post, but Dr. Kondratovich --

DR. REEVES: Correct, correct.

DR. NETTO: Very good.

DR. BERRY: Or something -- Marina. Thank you, Marina -- provided them. And it makes clear that the positive predictive value in the pre-menopausal cases is 34 percent, or something like that, which is really quite low. So I would, I guess, say several things. One is let's add specificity here, let's add positive predictive value, and for both the pre and the post-menopausal.

DR. FREEDMAN: Can I ask Dr. Berry a question, a statistical question?

DR. NETTO: Go ahead, Dr. Freedman.

DR. FREEDMAN: How important are the lower bounds here because some of them go below that 90

percent.

DR. BERRY: How important? Well, it reflects what the sample size is in that subset --

DR. FREEDMAN: How much attention should we give to them --

DR. BERRY: How important are the lower bounds? I think they're important. I mean, it gives -- how important is a confidence interval giving both ends of the confidence interval? So these are mostly estimates, what they were targeting when they were doing power is the lower bound. But at the end of the day, they get the data, and they provide us with what the confidence interval is, and I think that's appropriate. So I would do, you know, the 95 percent confidence interval.

DR. FREEDMAN: Actually, the question I was getting at is considering that 90 percent may be a cutoff for consideration of something being good or bad, is the lower bound a critical value that we should look at, we should comment on or express concern about?

DR. BERRY: No. Well, if I disagree that 90 percent is good or bad, if that were true, for example, we wouldn't be doing mammograms. So it depends on the utility. What is going to change the way we do things, and Dr. Moore indicates that things are so bad now that

this thing will change things in a positive way. And you wouldn't need a 90 percent, to be sure of 90 percent for that. So this is a clinical judgment based on what the status quo is.

DR. NETTO: Thank you, Dr. Berry. So it seems like that question will be the portion 2(d), "For the specified intended use population and indication, what is the clinical tolerable maximum percentage of patients who are falsely characterized as low risk? That's what you're asking? The one minus NPV because that comes at that 60 percent, and that's one concern of mine that I've mentioned earlier in term of the pre-menopausal having the one minus NPV up to 34 percent in some. So I think I would agree with the Panelist who mentioned no to the answer (a), and that should take us to (c). I would like to ask the Panelists on this side in term of what is the feeling on Question 2(a)? Dr. Julian?

DR. JULIAN: The problem I have is if it's to be used by a gynecologic oncologist to determine who is low and high-risk, that's fine, but I really don't think that any test should be used to refer people back into the community. Once they get to the gynecologic oncologist, they have a full-service physician who can handle the whole ball of wax there and sending them

someplace else where you don't know what you're going to get is a disservice. That's what I think.

DR. NETTO: Okay. Dr. Funkhouser?

DR. FUNKHOUSER: I would answer no to (a). My logic is that the only way we can do harm to women with LMP or invasive ovarian carcinoma, if we're persuaded by their arguments, is to refer the patient back to a surgical team that's less competent in their ability to deal with carcinoma when it's present. So, therefore, our goal should be for this test to minimize the negative predictive value. The negative predictive value of 95 percent observed with a lower bound of 92 percent, I would recommend that we raise that lower bound to 95 percent.

And, as you can imagine, that asymptotically approaches having every patient referred to the gynecologic oncologist, be operated on by the gynecologic oncologist, and in that extreme example, you don't need this test at all. So it ends up being in Dr. Julian's camp, saying if it's referred to the gynecologic oncologist, you've done no harm to the patient. They have optimal surgical care regardless of whether they have benign or malignant disease. I think --

DR. NETTO: But I would like to remind you,

it's not our job to say whether this --

DR. FUNKHOUSER: I understand. But, in terms of a recommendation for use of this test, in terms of triage back to the local treating physician, we want to minimize the number of patients who have LMP or invasive carcinoma --

DR. NETTO: Who can --

DR. FUNKHOUSER: -- being referred back. And the way to do that is to set a lower bound for the negative predictive value of at least 95 percent, if not higher.

DR. NETTO: Dr. Lichtor?

DR. LICHTOR: In some of my earlier comments, you may recall that I mentioned that I feel fairly strongly that we shouldn't be in the business of triaging patients. I feel very strongly about that. When you do that, you create monopolies, which means you're going to say, well, I'm the only one in this area who can take care of this problem, which may or may not be true. But it's really bad medicine.

I think all we should be doing is just saying this is what this test shows, and whatever you draw your limits on, I'll go any way on that. But the individual clinicians, whether they're oncology specialists or local obstetricians/gynecologists,

should be able to decide, is this something I can take care of or not, and we shouldn't be telling them who should they refer or not. We should just say this is what this test means and let them make the decisions. And it's not just based on this test. It should be based on the whole clinical picture and their surgical experience and lots of things.

So I would definitely take out for whom surgical intervention performed by a non-oncology specialist is appropriate because, to me, that's opening up the whole triage door, which I think is not the purpose of this committee.

DR. NETTO: So it seems like you're in consistent what we did in the first question?

DR. LICHTOR: Right, right.

DR. NETTO: And so it seems like the Panel is generally -- would out like to comment, Dr. Chan?

DR. CHAN: Dr. Netto, you probably should ask each Panel member to give their input on the question. I think a couple of them didn't say anything --

DR. NETTO: Go ahead, Ms. --

MS. HOLLAND: Well --

DR. NETTO: I think I guess --

MS. HOLLAND: I feel the same way about triage, but I may be thinking in the opposite

direction -- but, still, that has been my problem with the whole thing from the beginning is the triage issue. But I also, I believe the test belongs in the hands of the local GYN to make things flow towards the specialist. But the way it's written, it seems like it was to flow the opposite direction. That's my issue with it.

DR. NETTO: But that's how it's presented in -- the FDA for intention for use, so we can -- that's how --

MS. HOLLAND: But I think by changing the wording, as you already -- as we discussed on the first labeling issue, that takes out that problem for me.

DR. NETTO: Okay. Thank you. Ms. London, any comment, any additional comment?

MS. LONDON: No.

DR. NETTO: Any additional comment?

DR. BRACCO: No comment.

DR. NETTO: Anybody else? Yes, Dr. Berry?

DR. BERRY: So some of what I've heard confuses me. What is presented here in sensitivity and specificity and negative predictive value, whatever, that's the results of the study. So if you take this group, you know, what is their sensitivity, that group, what is their positivity, you know, what is the

negativity, what is the positivity, the question is that you guys are talking about is here is a patient and this patient has a value, and that value comes with not it's bigger than 13.4 or it's bigger than 27.3, or whatever it is, it's her probability is 53.9 percent, or whatever it turns out to be, and she's pre-menopausal and that's what this means, post-menopausal. And there you want to address the question of what I'm I going to do to triage or not this patient. So it's a very different thing from over the categorization within the study which talks about the scientific questions and does it do, you know, what it's supposed to do. And the latter part of these questions deal with that issue of, you know, the lower bounds stuff.

DR. NETTO: Okay.

DR. LICHTOR: Well, can I just say something?

DR. NETTO: Dr. Lichtor?

DR. LICHTOR: I think you're confusing the statistics with the clinical management.

DR. BERRY: Well, I thought that's what you were doing.

DR. LICHTOR: No, I'm not.

(Laughter.)

DR. LICHTOR: No, I don't. What I do with patients -- well, it's not my field, but I give them

the options. I say, you know, this is what the data shows, whatever data I have, and here are your choices and present it like -- and that's what I think should be done. It shouldn't be saying, well, it says that you should be referred to this person based on this number. See, that's what I object to. I think you should just present the data and say your probability is such and such. Your choices are you could go to an oncology person or maybe we could try it here. And here's the ups and downs of all those things. That's what you should tell the patient. Not this test says you should be referred one way or the other --

DR. BERRY: Oh, so --

DR. LICHTOR: That's where I draw the line.

DR. BERRY: Nothing I said did I mean to interpret it that way, and I agree completely. You give the number, and you say this is what it means, and you could be referred to whatever or not --

DR. LICHTOR: Well, I give the patient the option.

DR. NETTO: Excuse me just one a time. Thank you Dr. Berry. Go ahead. Do you have any --

DR. LICHTOR: I don't tell the patient one way or the other, although I don't make these decisions, but I make similar decisions. I tell them

here's your choices and then let them decide. I don't tell them the numbers say that you should go unless unusual circumstances. But in most of them they have choices, and they should make the choices. We can't make the choices because we don't have the data, based on what I've heard, to make the choices for them --

DR. NETTO: Thank you.

DR. LICHTOR: All we can do is tell them this is the data and here is your choices.

DR. NETTO: Thank you.

DR. LICHTOR: And I think that's all we should do.

DR. NETTO: Thank you.

DR. BERRY: I agree.

DR. NETTO: Thank you. Yes?

MS. HOLLAND: Well, I think that's the whole point of our problem with this is that it's presented as a triage system, when what --

UNIDENTIFIED SPEAKER: Yeah. Right.

MS. HOLLAND: -- we're trying to do is say we'd rather have it be a management tool, a patient management tool. I mean, I'm seeing what you're seeing. I'm sitting with my doctor, and he's telling me here's what we have. We have the CT scan results, and we have, you know, the CA-125 results, and now we

have the ROMA results. And what it means is, you know, you could potentially have this really bad malignancy, but we don't know that for sure. Here's what we can do. You can either stay in your hometown and do this thing, or you can go here to the specialist. And between the physician and the patient, we look at the evidence, and we figure out what's the next best step. So that's the problem. I want it to be a patient management tool --

UNIDENTIFIED SPEAKER: Well, so do I. I mean, that's --

MS. HOLLAND: But it's not written up as one.

DR. NETTO: Dr. Freedman?

DR. FREEDMAN: You know, I think informed decision-making is a very important thing in any patient relationship, but you have to be able to tell them what something means in order to say this is what you should do. I think most patients want to know what should they do in that situation when they're faced --

UNIDENTIFIED SPEAKER: Well --

DR. FREEDMAN: Especially when they're faced with a situation --

DR. NETTO: Just hold on.

DR. FREEDMAN: -- which is potentially curative or could affect their safety. They would

want to go to a physician who can say to them this is what I think you should do. And if you're going to use a test, you should be ready to interpret it and say either this test, I don't know what it means and I don't know -- it should influence your management, or I think it means this and you should go ahead with it.

I'm dead against using any type of test where it leads to confusion, more confusion for the patients, you know, he said this, that, should I go there or shouldn't I go there? I think we have to be more certain. And we're dealing with things that are not clear, where it hasn't been tested in the population. I know what you're saying, and it would be ideal if we could achieve that, but it hasn't been tested in that population. That's the problem.

DR. NETTO: Thank you. I would like to remind you that it's being scripted, so please don't talk over each other, and wait until I give you the chance, please. Yes, Dr. Ozols?

DR. OZOLS: I think the standard of care, if you really suspect somebody has ovarian cancer is to send that patient to a gynecologic oncologist. So an effective triage system would, in fact, be useful. I mean, there's already many barriers already. We have reasonably effective triage systems, and we already

know that 50 percent of patients who -- aren't operated on by -- even with the RMI assay, and so forth, aren't operated on by gynecologic oncologists. The overwhelming data suggests right now that those patients who are operated on by gynecologic oncologists do better than if they're operated by other surgeons, non-oncology specialists.

So I think the goal should be to get those patients to a GYN oncologist. Unfortunately, all the assay data we have now with this is the other way around. So, hopefully, if this was effective and it should be tested in that population in a trial to show that it is a good triage mechanism to get those patients to a gynecologic oncologist.

DR. NETTO: Thank you. So now that we heard from everybody, maybe we should consider answering the second question because we still have four more questions, and we're running out of time. So from what I'm hearing, and correct me if I'm not summarize what's the general feeling of the Panel, the answer to (a) is no, that it's not -- it did not prove that it's an adequate test in term of whom surgical intervention performed by a non-oncologist is appropriate.

So 2(a), the answer is no, which takes us to 2(c). So the remedies that the Panel was suggesting,

one of the remedy we already addressed is by taking that sentence out from the intention of use and by inserting that there is no data on the primary. Any obtaining additional data? Is that where we should suggest obtaining additional data in the primary population because it could help?

UNIDENTIFIED SPEAKER: I like that.

DR. FREEDMAN: I like that idea.

DR. NETTO: Is that something we can suggest as a Panel, question to the FDA?

DR. REEVES: You're free to suggest it.

DR. CHAN: Yes.

DR. NETTO: All right. Okay. We'll suggest it again. For question (d), so what's a tolerable one minute NPV, I think it's been mentioned by -- yeah, it's optimal if it's 100 percent, but knowing that is not achievable, I think by restricting it to oncologist, who are kind of mitigating against any injury that may happen by the false negative part. So should we --

DR. REEVES: I need a percentage.

DR. BERRY: Can I --

DR. REEVES: A percentage would be helpful to me in order to make a decision --

DR. NETTO: So --

DR. BERRY: Can I say --

DR. NETTO: Yeah.

DR. BERRY: I think the question is a bad question.

DR. NETTO: Did you like that answer?

DR. BERRY: The NPV is what it is. And the question is what are you going to do with it, and this is this dichotomy that I was talking about, about the study and science, and the individual patient. And for the individual patient, the NPV doesn't matter. What matters is what the test shows for her.

DR. NETTO: Correct.

DR. BERRY: So I think the question is --

DR. NETTO: Especially that it's --

DR. BERRY: -- ill-advised.

DR. NETTO: So the Panel does not feel one way or the other or should we go with --

DR. BERRY: I feel it's ill-advised.

DR. NETTO: Ill-advised.

DR. JASON: Well, you know, I think once the caveats are made in Parts (a) and (c), it obviates any need to address (d) and (e) because they're already getting the best care they can possibly get or the most sophisticated. If they go forward and do the additional studies that have been suggested, then you

need to address the issue of where do we put the cutoffs.

DR. NETTO: Okay.

DR. JASON: But this isn't an issue.

DR. NETTO: How does the Panel feel then, in part of this mitigation because the feeling that -- what I'm hearing from this side was that it's by stemming the potential return to general GYN care we're mitigating against this lower -- or higher false negative rate. So should not indicate as an aid in a decision to proceed to surgery or whom to be treated by? I mean, should we dare specify or is that --

UNIDENTIFIED SPEAKER: No.

DR. NETTO: No?

DR. FREEDMAN: I think we've done in the first question --

DR. NETTO: We took care of that?

DR. FREEDMAN: We've taken care of it I think to the -- I mean, outside of a new trial --

DR. NETTO: We --

DR. REEVES: I'm sorry. I'm having difficulty hearing you. Could you --

DR. NETTO: The feeling is that by answering the first question and the first two portion of the second question that we've mitigated against -- the NPV

is what it is and -- sorry.

DR. GUTMAN: It would be very helpful for us to know if it -- if the members of this committee believe that this product is safe and effective with a change in labeling of some sort or if it's safe and effective contingent upon trying to get more data.

DR. NETTO: Okay.

DR. GUTMAN: That would really be helpful for us to understand, whether you think a labeling fix will make this safe and effective or whether you think it needs more data to be safe and effective, and if you could canvass the committee for that question, we would be very grateful.

DR. NETTO: So the mere recommendation of obtaining additional data would not satisfy that because, I mean, this is what the Panel is --

DR. GUTMAN: Well, it makes a big difference to the Sponsor. If you say that they need more data, then they're going to have to do additional studies. If you say they can fix this through a labeling and it can be used with a particular labeling fix, then they have a product which is probably safe and effective and can be cleared.

DR. NETTO: Okay.

DR. GUTMAN: So that's the most important

question, I think, that's on the table.

DR. NETTO: Okay. Thank you for clarifying.

DR. BERRY: It wasn't --

DR. NETTO: Yes, Dr. Berry --

DR. BRACCO: May I? It wasn't on the table until you put it on the table, Dr. Gutman. This question is not the question that you asked. The one that you asked, I agree, is absolutely the right one.

DR. OZOLS: And the only --

DR. NETTO: Yes?

DR. OZOLS: And the only way to answer that and to get -- is to do a clinical trial. I don't know. You can wordsmith the label, but the data is only available from a prospective clinical trial -- the population where it is likely to be used, and that is in the community situation as a referral to oncology specialists. And then we know. I mean, how bad if -- and then one minus NPV is just a number. If it translated in a randomized trial, we would know whether that leads to a significant deleterious outcome.

DR. NETTO: Dr. Bracco?

DR. BRACCO: I think there are two paths that we haven't clearly answered here. One is that we need additional clinical data, and this device cannot be released into interstate commerce until that data is

obtained. The other is that we release the product or suggest to FDA that it be cleared based on the existing clinical data with all the caveats and the labeling that we propose. And I think it's important for the Panel to give FDA clear direction in that regard.

DR. NETTO: Okay. Go ahead.

DR. FREEDMAN: I would be okay with the idea of the labeling, additional labeling making it safer than it was without the -- but how safe it needs to be, how safe is safe, that's a difficult question to answer without another study. But, certainly, it's going to give a higher level of safety with the additional labeling that we discussed under Question 1.

DR. REEVES: I'm sorry. Could you move closer to the microphone? We're having difficulty hearing you.

DR. FREEDMAN: I say it would make is safer with the additional labeling that we -- and warning that we advised in Question 1. Ideally, one would want a new study. But in the absence of that, and maybe that will be something forthcoming later on, I think that what we have here potentially is safer than it was without. I prefer, personally, I would prefer another study where they looked at that population from where these patients would come.

DR. NETTO: Dr. Berry?

DR. BERRY: So I agree with Dr. Ozols that his concern about the use in the ordinary practice, and I think it's going to be used off-label. I think it is safe and effective for the population that they've proposed. So I would follow the second option. But I would mandate because I think it is a serious concern, I would say that there has to be a study that looks at how is this going to be used in ordinary clinical practice, and is it -- does it provide more benefit than harm in that group. So I agree with both Drs. Freedman and Ozols.

DR. NETTO: So the rest of the Panel? Yes, Dr. Funkhouser?

DR. FUNKHOUSER: Dr. Berry, is it true that the negative predictive value is a function of where they set their cut point for the assay?

DR. BERRY: Yes. So can I answer that?

DR. NETTO: Yes.

DR. FUNKHOUSER: So if that's true --

DR. BERRY: Yeah --

DR. FUNKHOUSER: -- and if it's also true that the only way that we can harm these patients is to refer them back to their local gynecologists, who we've heard elegant arguments do give them worse care and a

worse outcome than if they stay with a gynecologic oncologist, within this narrow definition of the use of this test, for a patient sitting opposite a gynecologic oncologist, he presents them with a result, the only way that we can harm that woman is to give her a low-risk designation when in fact she has cancer, is that correct?

DR. NETTO: Correct.

DR. FUNKHOUSER: So the way to minimize that probability is to reduce the negative predictive value to below 5 percent. Do you agree with that?

DR. BERRY: So you could do that by moving the cut point.

DR. FUNKHOUSER: Changing the cut point for ROMA --

DR. BERRY: But you'd have to move the cut point.

DR. FUNKHOUSER: That's right.

DR. BERRY: We haven't been asked to move the cut point.

DR. FUNKHOUSER: Well, we're making recommendations to maximize the benefit and reduce the risk to these patients, so if you don't want the gynecologic oncologist to operate on 100 percent of the patients that they're talking to, then your triage

option is to minimize the harm. And to do that, you should minimize the negative predictive value of this test, do you agree?

DR. BERRY: So the only way you can do that is to move the cut point, and we haven't been presented with, you know, a flexible cut point. What we are seeing is that they're going to provide the actual value and an interpretation of what the cut point was in terms of the specificity, sensitivity, and things like that. And implicit in that was the triaging issue, but it was set at an arbitrary value of 75 percent specificity --

DR. FUNKHOUSER: Arbitrary is the key word.

DR. BERRY: So I take it when they say negative predictive value that, in fact, the FDA is thinking about having them change the cut point. That's the only thing it could mean. But we haven't been approached with that question.

DR. NETTO: Is that something under the purview of this Panel, is to suggest changing the cut point to minimize the NPV?

DR. REEVES: Not entirely.

DR. NETTO: Go ahead.

DR. REEVES: There are multiple people here. I will move out of the way.

DR. GUTMAN: You can make any recommendations you want. They can be reasonable. They can be wild. You make what recommendations you want.

DR. NETTO: Okay.

DR. FUNKHOUSER: They must be interested in the negative predictive value. Otherwise, they wouldn't ask Question 2(d), which asks for what we would tolerate as a one minus NPV.

DR. NETTO: Okay. So what's the general feeling at least so we can stick a number to that one minute --

DR. JASON: I don't feel we have the data to come up with that. We don't have data to know what the benefits and risks are in that setting. Not everyone who gets surgery is going to necessarily have need it, but they're in the best possible hands. So we'd need more data in terms of what types of surgery, what approaches, and what the outcomes are before we could even deal with this.

DR. NETTO: And as was suggested, should the -- a clearance await that additional data, both in the primary or in the same setting or should it be the --

DR. JASON: Well, you're not completely wrong. By the time we're done, I'm not sure how the