oncologic surgeon is going to deal with this. It certainly, if it's truly done with the now narrow definition, it's perfectly fine. I just don't know what they're going to do with it.

DR. BRACCO: There actually is one other option, and Dr. Gutman or Dr. Becker, maybe you can answer this. And I know it exists in the PMA world, but is there any way we can -- the option exists to have this device cleared with a requirement for a post-market study. And you're saying no --

UNIDENTIFIED SPEAKER: No, it's not a PMA.

DR. REEVES: No, it's not an option.

DR. BRACCO: Okay.

DR. REEVES: It's only available for products that are PMA.

DR. NETTO: So in order to summarize, what's the general consensus in term of clearance with strong recommendation for necessity of additional data versus awaiting additional data?

MS. HOLLAND: I'd like to see it cleared, but with clear limitations stated in the packaging. But the reason for that is because I agree that what's available to GYN oncologist for ovarian cancer is slim to none right now, and this is a new thing that can be well used. I also agree the only way we're going to

hurt somebody is by taking someone who has cancer and sending them to the wrong doctor.

DR. NETTO: How about the rest of the Panel members?

DR. OZOLS: I would prefer to wait until we have more data. If it comes down to approval or wait until more data, I would be in favor of more data.

DR. NETTO: Does that sound --

DR. FREEDMAN: I feel, I mean, more data would certainly satisfy me more.

DR. NETTO: Dr. Jason?

DR. JASON: I'd have to defer to the people who have experience with the other assay. If they know that it's been misused that long, there's every reason to believe this one would be, too, in which case waiting for more data would be the more appropriate route to go.

DR. NETTO: Thank you. Dr. Julian?

DR. JULIAN: I would like to know what happens to people who are referred back in the community. That's what this is all about, and there's no information on those people.

DR. NETTO: Because there wasn't any referred -- in this part, but you were expecting that?

DR. JULIAN: Yeah, that's what it's all

about, isn't it --

DR. NETTO: So --

DR. JULIAN: Getting referred back --

DR. NETTO: So your answer is awaiting more data or --

DR. JULIAN: Yeah.

DR. NETTO: Awaiting more data? How about Dr. Funkhouser?

DR. FUNKHOUSER: What are my choices, Dr. Netto?

DR. NETTO: The choices that were given to me is clearance with stipulations in the labeling and changing the labeling to assure safety and efficacy versus requests for data and the clearance would be contingent on coming back and presenting more data in terms of the primary or what happens with referred back to the GYN community.

DR. FUNKHOUSER: With respect to the narrow intended use of triage from a GYN/ONC practice back to a local gynecologist, I think we have adequate data to know what their negative predictive value is at a specific -- at a certain specificity. If you want to expand the FDA process to consider the opposite direction of triage; that is, from local community GYN practice to the GYN/ONC practice, that's the more

likely use of the ROMA test, but they haven't addressed that. Is that what you're talking about getting additional data on?

DR. NETTO: And also on when it's used in the exact setting that they're suggesting, what's going to happen in term of some patients being referred back. Although we took that sentence out, but that's not guaranteed. But, again, it's not our job to enforce that part. But if you're feeling that the one minus NPV as it stands based on the data is -- it's not good enough, then maybe if you would feel better about having some more data, then --

DR. FUNKHOUSER: I'm satisfied with the dataset that they have, but I don't think that it's clinically realistic. I think that the clinically realistic scenario is the gynecology practice use of ROMA to define high-risk patients for referral to gynecologic oncologist, not the other way around. But within the narrow purview, today's discussion, related to GYN/ONC triaging back to the gynecologist, I think there is enough data, and I think that the NPV should be less than or equal to 5 percent lower limit, that the cut point should be adjusted so that there is minimal risk to women being referred back when, in fact, they have LMP or carcinoma.

DR. NETTO: All right. Thank you.

Dr. Lichtor?

DR. LICHTOR: I would say that I think ROMA should be approved for use by only gyn-oncology surgeons as part of the management of patients with ovarian cancer and not tell them anything about who should be referred where. And the second part, I would say more data needs to be done for any other use of it, which would include people in the community and non-oncology people or family practice or obstetricians.

DR. NETTO: Dr. Berry?

DR. BERRY: This thing about off-label use, I mean, I don't think that we should be recommending not clearing something because people did some bad things in other circumstances. People do bad things in drugs, the off-label use of drugs is probably more than the on-labeled use of -- there's lots of off-label things. I think it's incumbent on us and it's incumbent on the FDA and the company to make it clear what the data were --

DR. NETTO: Okay.

DR. BERRY: And that it was a particular circumstance, you know, that patients who were recommended for surgery or whatever the issue is and that it can and it should be approved for that with

caveats about -- very strong caveats about what it's not approved for.

DR. NETTO: Okay.

DR. BERRY: And it think it would be incumbent on the company, if not the FDA, to do the study in general practice. Okay. So --

DR. JASON: With the calcium 125, was it initially recommended only for a subgroup or was it just put there?

DR. NETTO: It's not recommended for benign versus malignant. It's not approved for that.

DR. JASON: I see.

DR. NETTO: So it's not -- nothing to compare to. So it seems like the general feeling is to clear it for specifically the way it was studied in the pivotal study with strong stipulation that any additional use should await the data from a primary care setting study.

DR. FREEDMAN: Can I just make a point about why I think additional data would be helpful? If you take the CA-125, which has been around for many years, we're still learning about the specificity. We're learning every day about medical conditions that can cause elevation of that test. We have relatively little data in comparison to the very extensive

literature and studies that have been done with the LM marker. And its time is going to of course be important in collecting that data. So particularly out in the community where these conditions are quite prevalent, hypothyroidism, cardiac disease, hypertensive disease, and so forth, which could impact on the usage of this test. I think that should be considered as a factor which should encourage additional studies with the test. We don't know.

DR. JASON: Can they do post-marketing monitoring to see who is buying these kits?

DR. NETTO: My understanding that we're not --

DR. JASON: That's not --

DR. NETTO: That's not a PMA, yeah. Go ahead.

DR. CHAN: So does the Panel think that the one minus NPV as currently stated is acceptable, tolerable? I know that --

DR. NETTO: Five percent was thrown in. The rest are refusing to give acceptable level. Five percent -- and the feeling is acceptable if really the guidelines are adhered to in term of patient staying with the guideline.

DR. BERRY: Dr. Netto, can I say that my

reason for not saying much about the NPV is that it implies a decision that you're going to do something. And so I've heard lots of negatives regarding -- I don't want to recommend it, but triaging -- I wouldn't send it back if -- and so there's lots of fuzziness, ambiguity, in my mind, as to exactly what the decisions would be. If you say here's the decision. We're going to recommend that the patient go back to the community oncologist to get surgery for what is probably a benign growth --

DR. NETTO: Then you would look at --

DR. BERRY: Then we can talk about NPV because it's not -- it has an action associated with it, and we can weigh the cost one way or the other. But until we come with a particular decision, this is what we're going to recommend it for, then the NPV doesn't make sense.

DR. NETTO: And I think the comment is we're mixing a false negative with NPV so -- okay.

DR. JULIAN: We have taken out or recommended that the issue about triaging back to the gynecologic oncologist not be in the label.

DR. NETTO: Exactly.

DR. JULIAN: So I agree. The NPV in that case is irrelevant.

DR. NETTO: So it's acceptable --

DR. JULIAN: They're going to be operated on by the gynecologic oncologist. Whether it's 2 percent or 5 percent, he's still going to be the one operating on her, he or she.

DR. NETTO: So what that study found --

UNIDENTIFIED SPEAKER: Is there a he with ovarian --

DR. JULIAN: The gynecologic oncologist he or she.

UNIDENTIFIED SPEAKER: Okay.

DR. NETTO: Okay. Let's go back. And as far as the maximal percent of patients who are falsely categorized at high-risk, I think that's less of a concern, so it's acceptable to where it is in the study. Question Number 3?

DR. REEVES: The pivotal study presents no data or analysis of interaction between the Predictive Probability (ROMA) results and other clinicopathologic variables (for example, patient's symptoms, physical findings, imaging) for detecting the presence of ovarian malignancy. Therefore, from the pivotal study, no formal demonstration is possible that use of the test together with currently used clinicopathologic data is either more or less advantageous than using the

test alone or using other clinicopathologic data alone. Given the pivotal study data:

(a) Can clinicians knowledgeably and safely integrate Predictive Probability with other clinicopathologic information available to them for the intended use population?

(b) If "yes," how can this be accomplished and how might test labeling facilitate safe and effective use of the test result along with other clinicopathologic information?

(c) If "no," how can the Sponsor address this in labeling or through obtaining additional data?

DR. NETTO: Okay. Dr. Funkhouser?

DR. FUNKHOUSER: No data?

DR. NETTO: No data? Dr. Julian?

DR. JULIAN: I would say, yes, you can use it, I mean, if you have an examination that showed you this is fixed and stuck and feels like cement. I mean, you can certainly use everything you have available to make your decision. I don't see how you cannot integrate if you're going to use this, how you couldn't integrate it with the other findings.

DR. NETTO: But as far as, I guess the question is, as far as the intention to use, did the study data provide any data in term of how to integrate

it, and is there some need of changing the wording on how to integrate it. So --

DR. JULIAN: Well, the data they provided was from other studies. Not from theirs.

DR. NETTO: Okay. So the answer is no for A?

DR. BERRY: So can I --

DR. NETTO: Dr. Berry?

DR. BERRY: What I think this question is, is when you calculate the Predictive Probability, it's based on the patients in the trial. And the patients in the trial are a heterogeneous mix, given, of course, that they have a particular condition. And so if you wanted to then say, well, let's bring in other information that we know about a patient, how can that modify the Predictive Probability, you can't really do it because the Sponsor hasn't provided the individual characteristics. And so I think the answer to the question is no, but I assume -- and the Sponsor could probably tell us. I assume that there were no other covariates that were predicted.

DR. NETTO: We don't know that.

DR. BERRY: We don't know that. So the answer to the question is no. We can't update it because --

DR. NETTO: Thank you.

DR. BERRY: Because we don't know what the data were in the individual trial.

DR. NETTO: Thank you. Dr. Ozols?

DR. OZOLS: I agree.

DR. NETTO: Everybody else agree? So anymore comment -- so it seems like the answer is no as far as availability of data to correlate with the clinicopathologic, and that was why the test was studied as a standalone. And then, so, that's the answer for 3(a), and that will take us to 3(c). If no, how can the Sponsor address this in labeling or through obtaining additional data? Any suggestions on --

DR. FREEDMAN: Well, we've heard about the secondary objectives, the secondary objectives that they have and they're supposed to have the data, but that has not been presented. It certainly wasn't presented to us in detail for us to look at. I know there was some -- one or two slides presented, but I'm not sure if the FDA has had access to that data fully where you indicated that 80 percent of the data was available, 20 percent was not.

DR. CHAN: According to the Sponsor, the data was not collected, and for the 80 percent that was, you know, was analyzed later on for the imaging, that was later on --

DR. NETTO: That was the imaging --

DR. CHAN: Information. And it's only on imaging, and they don't have, you know, other data.

DR. NETTO: Is the feeling of the Panel that such data should be collected and as part of the remedy or remedying through changing the labeling, clarifying more the fact that it's a standalone test and it's -- it has not been evaluated in the setting of -- in conjunction with any of the other clinicopathologic variables. Should we be clear about that in --

DR. JASON: Well, I think one reason to say that more data is needed is this test will not be free, and some of the information we've not gotten is family history, some of the details on the imaging, things that in their own packet they said were important, none of which cost anything. So if we're talking about what are the best predictors, it would be worthwhile having the additional data and seeing does this add to that, even in the restricted setting of just being at these referral centers.

DR. NETTO: Yes, Dr. Freedman?

DR. FREEDMAN: I think that the -- seems the members' comfort level is where the test is used in an oncologic setting where they know that other factors will protect the patient. But to approve it as a

standalone test would make me uncomfortable especially if it became emphasized that it was a standalone test. And more data would be -- I think might solve that issue.

DR. NETTO: Dr. Berry?

DR. BERRY: So can I get a clarification? What I understood from what Dr. Gutman said is that if we ask for more data and they decide that more data is necessary, then it's out, it's not cleared, and that they can't do -- they can't mandate a post-marketing study.

DR. NETTO: Can we get a clarification on that because it seems like on several point we feel that we need more data. Does that --

DR. GUTMAN: That's exactly the question that there's either a need for more data before you think it's wise for us to find this safe and effective with some intended use as stated or modified or -- well, if you need more data, then we should probably not clear this --

DR. NETTO: So it's mutually exclusive?

DR. GUTMAN: Yes, yes.

DR. NETTO: So, basically, what we did in Question Number 2 --

DR. GUTMAN: You can't have both. You can't

have both.

DR. NETTO: You could do both?

DR. GUTMAN: No, you can't have both.

DR. NETTO: Yeah, so then --

DR. GUTMAN: You either need more data --

DR. NETTO: -- we've already broke that rule in Number 2, so, basically, when we're recommending more data, we're basically saying do not clear until that data is looked at --

DR. GUTMAN: Not at this time, not until the new data comes in --

DR. NETTO: Okay.

DR. GUTMAN: And we'd have to decide --

DR. BRACCO: But an option that you can use is to put this in as a limitation in the labeling. And then if the Sponsor wants that limitation removed at a subsequent time, then they would have to provide the clinical data to the FDA to get that removed. So it is still possible to have the device cleared if you feel that's appropriate with this limitation in the labeling.

DR. NETTO: The problem is that the feeling is not be mentioned as a limitation is in the language of intend to use, so there is a strong feeling about these data, need for these data to the point that they

need to be put in the intent to use rather than the limitation, if I'm reading the Panel members correctly. Because it seems like, going back to your point, that is, it's mutually exclusive, the mere fact that we've already recommended that we need more data in the primary in the previous question, we're pretty much telling the FDA do not clear until you see that data because we do not have the power of saying -- it's not like a PMA and saying go back post-approval and look at the data.

DR. FREEDMAN: I'd like to ask a question of the FDA, and that is, is there a precedent for approving an in vitro device as a standalone? Is there a substantial --

DR. REEVES: Yes, yes.

DR. NETTO: Dr. Berry?

DR. BERRY: Can I say something as a statistician, finally?

DR. NETTO: You haven't said anything as a statistician?

DR. BERRY: This issue is huge. I mean, it's to address the question of what is the impact of additional covariates as it affects this. To say that we want data that's going to address this question is going to be a big study, necessarily, but it's the kind

of thing that people do naturally when something is approved. So they start look at, okay, here's ROMA, and now I've used it in my population. I have these other factors. Do they add to ROMA -- a ROMA -- I guess a good -- I don't know. But do they add to it so that we can improve the Predictive Probability based on these other characteristics. Possibly, the biomarkers like we see here, but also, possibly, clinical characteristics.

DR. NETTO: That's correct. I believe, in my opinion, that's correct, as long as there is no harm and there is no safety concerns meanwhile. So if the feeling is it's safe as is, then collection of additional post data after clearance --

DR. JASON: Although you are --

DR. BERRY: I'm saying not --

DR. NETTO: But that is a concern --

DR. BERRY: I'm saying other people like academic centers will --

DR. NETTO: There is concern -- if -- concerned about the safety --

DR. JASON: Although you are going somewhat backwards because these other factors are known to influence it, and now you're adding one.

DR. NETTO: Yeah.

DR. JASON: So what you're doing is a little bit backwards. But you could do that.

DR. BERRY: Backwards only because time happens to go in the direction --

DR. NETTO: We will have to move on. Excuse me. So I would like to get a feeling from the Panel whether -- how strong is the feeling about additional data in term of covariates and integration with clinical and whether this can be remedied alone by changing any of the wording or whether data is needed. And if data is needed, so, basically, we are recommending not clear until that data is collected. So what's the general feeling? Dr. Ozols?

UNIDENTIFIED SPEAKER: I'm going to put my vote in more data --

DR. OZOLS: More data.

DR. NETTO: More data? More data? More data, Dr. Funkhouser?

DR. FUNKHOUSER: If you want the clinician to integrate the predictive --

DR. NETTO: You have to do that --

DR. FUNKHOUSER: -- coefficient with the clinical and radiographic features, you're going to need to find out if it's independent or whether it covaries with already known clinical radiologic

variables.

DR. NETTO: Dr. Lichtor?

DR. LICHTOR: I think it's okay for the limited use that I mentioned, which is just in the hands of the gyn-oncologist to use as he or she feels reasonable based on the clinical data that they must have because I think if you tell them you need more data, one, that's very expensive, and it's not really going to address the question that they asked, which is a very limited use for this. So I would just say it's okay for the very limited use, and if you want to use it for anything more, you got to get more data.

DR. NETTO: The problem is with the very limited use, you're basically saying regardless of the test, go ahead and proceed with a surgical oncologist. That's the only time you're feeling safe about it from what you're saying.

DR. LICHTOR: That's what I say.

DR. NETTO: And as opposed to a standalone test, which is the way this test -- the pivotal study was presented, they didn't even collect additional data -- covariates.

DR. FUNKHOUSER: Well, not that we know of.

DR. NETTO: Well, they're saying the only collection they collect is 80 percent of the imaging.

So my feeling is there were a lot of clinical data that was not collected. So for us --

DR. LICHTOR: Well, that's what I think, which means it would be --

DR. NETTO: So for us to make a recommendation about how to integration is baseless. And so if the general feeling -- I would go with that general feeling, if that's the general feeling that more data needs to be collected in term of covariates --

UNIDENTIFIED SPEAKER: I vote against. I vote with Dr. Lichtor.

DR. NETTO: We're not voting. It's just --

UNIDENTIFIED SPEAKER: No, no, but you know -- I'm using vote in the English sense.

DR. NETTO: I would think as the general consensus is that more data is needed in term of the covariance clinicopathologic collection of data, and that means it should await clearance until that data is because it may give the suggestion that this is a standalone and knowing that we cannot enforce the use in the primary care, that's -- we're opening another door, potentially, for using it as a standalone from the primary care in deciding who goes to the oncologist and who doesn't. And we don't want that, not before we

know based on the integration --

DR. BERRY: Yeah, but the way they did it, all the patients had already gone to the oncologist --

DR. NETTO: Correct.

DR. LICHTOR: So, to me, you can just say, okay, well, that's how they did the study. That's all we're going to approve. If you want to use it any more, you got to do all this more work. But in fairness to them, that is going to be a very expensive study to do.

DR. NETTO: If there is enough safety concern, I would go --

DR. BERRY: Can I add to that? If they had all of the clinical data in this study, they wouldn't have been able to answer this question. They need huge databases to answer this question. And so you're asking, essentially, you know, climb that wall, it's 1,000 feet high.

DR. NETTO: I'm not. The Panelists are the ones who have that feeling. So I'll go with the general consensus. I think that was the answer to --

DR. REEVES: Okay. Thank you. Question 4:

Please discuss and advise concerning the relative clinical impact of mis-assigning a LMP tumor or low-stage epithelial ovarian cancer compared to mis-

assigning a high-stage cancer.

DR. NETTO: Go ahead, doctor --

DR. FREEDMAN: I mean, I think we mentioned this earlier, and that is that early stage disease is a critical area because those are the patients that survive best if they are properly treated and if they are properly monitored and managed. And I think that was a little concern of mine that when you looked at the performance of the test, there were a number of patients with LMP. Of course, we don't know how many of these had invasive implants. But even if -- I know there's a lot of controversy about treatment in regard to LMP with invasive implants. But even the monitoring is critical by someone with an oncology background. So that would be my concern.

DR. NETTO: Go ahead.

MS. HOLLAND: Well, I don't think it's as much of a concern if you're pretty much referring everybody on to the specialist.

DR. FREEDMAN: Well, but the question was not --

DR. NETTO: That's not the question. The question is what's --

DR. REEVES: Mis-assigning --

DR. FREEDMAN: Yeah.

DR. REEVES: It's mis-assigning, it's making a mistake.

DR. NETTO: Correct. Knowing that in the pre-menopausal there was a significant portion of that LMP low-stage that was mis-assigned, what's the clinical impact --

MS. HOLLAND: Oh.

DR. NETTO: So they want our help in communicating the concerns we have in term of is that a big deal to mis-assign those LMP or that's not --

DR. FREEDMAN: -- for those patients as individuals.

DR. NETTO: It is, yeah. So the answer is -- let me ask the rest of the Panel. Dr. Berry, do you have any comment on that?

DR. BERRY: No, I don't.

DR. NETTO: Dr. Ozols?

DR. OZOLS: Mis-assigning an LMP because their natural history is so long -- so good and few patients die of LMP tumors whether it's a Stage 1 or Stage 2, it's probably less important and doesn't impact upon our management, whereas mis-assigning a low-stage tumor, like Dr. Freedman talked about, is a huge mistake, and you want to make sure that that patient gets appropriate treatment based upon their

stage. So if it's a cancer, you really want to make sure that it is a correct stage, low --

DR. NETTO: Thank you. Dr. Jason?

DR. JASON: No --

DR. NETTO: No comment? Dr. Julian?

DR. JULIAN: I agree with Dr. Freedman.

DR. NETTO: Dr. Funkhouser?

DR. FUNKHOUSER: Accurate staging drives prognosis so the patient should be staged if they're LMP or above. Errors in the opposite direction, that is, overcalling benign as LMP does no harm to the patient.

DR. NETTO: Okay.

DR. LICHTOR: I would just say I don't really understand the point here because all the patients in this study underwent surgery. So this doesn't seem like it would make any difference. Now, it will make a difference if you're going to open up this study to the community, and that data, as I said, is not there and it shouldn't be approved for that.

DR. NETTO: Okay.

DR. LICHTOR: For the limited use of the study, I don't think is an issue.

DR. NETTO: But as far as the question is really, is mis-assigning LMP and low-stage compared to

high-stage, what's the feeling about that?

DR. LICHTOR: Well, I agree with everyone else said on that.

DR. NETTO: Okay. And I do, too. You could argue the LMP, but mis-assigning a low stage, this is opportune time the people you want to catch because you really make a difference in their lives. So I would not think it's any less significant than mis-assigning high grade, and I think that's the general consensus of the Panel.

DR. REEVES: Question 5: Please comment on the practicality and medical impact of converting an ongoing operative procedure from non-oncology to an oncology if malignant tumor is unexpectedly found. Is such intraoperative conversion a viable path to mitigating the impact of false negative test results?

DR. NETTO: Start with you, Dr. Ozols.

DR. OZOLS: I mean, I think that's something only a gyn-oncology surgeon could answer. That's --

DR. NETTO: You defer?

DR. FUNKHOUSER: I defer to the gynecologist and the gynecologic oncologist.

DR. NETTO: Dr. Julian?

DR. JULIAN: Yeah, there's a huge difference. I mean, before there were gynecologic oncologists in

1976, there weren't a lot of them around, so I had to do a lot of cancer. And if you're not set up and ready to go with whatever it is needs to be done -- for instance, if you had a little tiny Pfannenstiel incision and you find this patient has sub-diaphragmatic, good luck. The average gynecologist cannot resect large or small bowel, cannot bring out a loop colostomy, cannot strip diaphragms. They may not even know if this is a mucinous cyst adenoma, I should take out the appendix, too. They don't know these things, so I think the difference is absolutely huge.

DR. NETTO: All right. Dr. --

DR. FREEDMAN: Well, it's obviously important if the patient hasn't been properly prepared, doesn't know, goes into surgery, doesn't know, comes out finding that they've had a lot of surgery done that they didn't expect to have. It's already something that can impact on their relationship with the physician. And also the fact that they may not -- since they're not adequately prepared, they may not be able to have the type of surgery that they should have. For example, bowel resection, unprepared bowel resection, there's a higher morbidity there. And sometimes the spleen is removed. There's risk of infection. All of these factors could come into play

in an unprepared patient.

DR. NETTO: So --

DR. FREEDMAN: So --

DR. NETTO: The medical impact is serious or --

DR. FREEDMAN: It could be serious, yes.

DR. NETTO: Dr. Ozols?

DR. FREEDMAN: Even if they're --

DR. OZOLS: Yeah, I mean, well, Dr. Moore mentioned that he sometimes can pop in when there is, you know, when a GYN guy is doing the surgery and all the sudden he finds a malignant tumor unexpected and he can help out. That happens, and that's great. But the number of times that happens I think is not very common. And I think most times a malignant tumor is unexpectedly found a gynecologic oncologist is not hanging around the corner ready to jump in the OR. And so they will require another operation. So to do two operations when you can avoid that is obviously preferable.

DR. NETTO: Any additional comments? Yes?

MS. HOLLAND: I think this what some of us referred to as the peek and shriek, when you open up somebody and peek in and see what's there and then shriek because it's not what you expected, it's way

worse that what you expected, and that's what we don't want to see happen, and that's why we want people referred to the specialist. No peek and shriek.

DR. NETTO: Anybody else? Any additional comments?

(No response.)

DR. NETTO: So the answer, and correct me if I'm not rephrasing correctly, the practicality and medical impact, that it does have a serious impact, medically, and that's something that is best to be avoided. And exception of the settings where a medical oncologist is on standby, which the feeling is that that's not a common situation.

DR. REEVES: Okay. I apologize for taking so long.

Number 6: The Sponsor performed re-determinations of menopausal status of 54 subjects in the pivotal study (using additional classification rules incorporating the use of FSH measurements according to local laboratory practice). Thirty-nine patients originally classified as post-menopausal were reclassified as pre-menopausal. Please discuss and advise concerning the general reliability of methods for assessing menopausal status, as it might affect test results. Are specific instructions for

determining menopausal status necessary to ensure safe and effective performance of the Sponsor's test?

DR. NETTO: Dr. Freedman, you've commented on that.

DR. FREEDMAN: I've commented on this before, and I think in this particular case, they used the FSH to facilitate the completion of the study. But I would not like to see FSHs now added to this assay, which might complicate things further. But I think that a reasonable definition that's accepted, the endocrinologist, the gynecologist, should be stated somewhere in the literature that is going to be provided, that would be provided to patients.

DR. NETTO: Dr. Ozols?

DR. OZOLS: Well, you just said you're not in a business of dictating practice, and, you know, I don't think it's -- you're going to have different viewpoints on what is exactly menopausal status, and it's a little bit ambiguous. But I think you have to leave it at that. It didn't make huge difference here, I don't think. So I would not put this in the labeling.

DR. NETTO: Dr. Berry?

DR. BERRY: I mean, of course, I don't have anything to say about how you should determine it, but

it has a huge impact on the model. If you're a 48-year-old woman, and, you know, you haven't had a menstrual period for three months or something like that, it's not clear if you do the pre-menopausal version, you could get, let's say, a 15 percent, and that's in the danger zone. If they did the post-menopausal, you could get a 25 percent, and that's not in the danger zone even though it's bigger. It's a little bit strange. And it could have a more dramatic impact than that.

I think it behooves the Sponsor to go back and look at that marginal case and say does it matter which version we use, in terms of the size of the Predictive Probability. And, hopefully, it doesn't matter much. But I think it's going to -- it could matter greatly.

DR. NETTO: My understanding that it didn't matter in the set of 38 because we asked specifically that question. And it didn't. But that doesn't mean that didn't --

DR. BERRY: Didn't matter in what sense?

DR. NETTO: In term of when they were classified as pre and then reversed to post, or vice versa, it did not matter, which is surprising, given the differences in the formula. But in this specific

group of 38, but as a statistician, is that enough group to generalize from because there are many patients that graze --

DR. FREEDMAN: If I can add, you know, the results of the study don't advise on how to use the FSH in any of these patients because endocrinologists might want to repeat samples because you get the cyclical change. And, in other words, if you start to use a test which really hasn't been -- now it's being added to another test, which is for a different purpose, I'm just concerned that we conflict things. Right now, we have a reasonably accepted definition of the menopausal. And if there is a patient that doesn't meet those criteria because the history is not available, it might be safer not to use this particular test, not to use the test before us, than to use it, and to use it incorrectly. And, here, I also I would get advisement from endocrinology experts as to whether it is appropriate, you know, to use the FSH, and, if they do, how they should use it.

DR. NETTO: Dr. Funkhouser?

DR. FUNKHOUSER: There are marked differences in prevalence between pre- and post-menopausal females for ovarian carcinoma and LMP as well. For that reason, if none other, we should use their criteria,

including use of FSH if we're going to use their cut points in this model. Unfortunately, they haven't addressed intra-laboratory reproducibility for FSH measurements. I think that could be described. And in the brochure, it should give the clinician a way to use the FSH measurements to decide pre- and post-menopausal when they integrate it with their clinical information.

DR. NETTO: Dr. Julian?

DR. JULIAN: There's any number of tests that you could do to determine menopausal or not menopausal. It isn't limited to this, but this test is fast, it's relatively well-accepted, and it's as good as anything else they could have done in a situation where you shouldn't hesitate to get something going.

DR. NETTO: So you're okay with the way --

DR. JULIAN: Yes, I think they did --

DR. NETTO: Dr. Lichtor?

DR. JULIAN: -- what they should.

DR. LICHTOR: I would defer to the others on this.

DR. NETTO: Sure. And so it sounds like it's okay the way it was listed. Whether the FDA feels they need the consultation from an endocrinologist regarding whether the effectiveness of one-time FSH at the intra-laboratory variation to put something in the wording,

that we leave it up to you. But as a basic premise, it's okay the way it is.

DR. REEVES: Okay. Thank you.

DR. NETTO: We have now -- if there is any further comment or question?

(No response.)

DR. NETTO: We have now provided FDA with our responses to their questions related to the HE4-EIA immunoassay ROMA. The December 3, 2008 meeting of the Immunology Device Panel is now adjourned. Thank you very much everyone.

(Whereupon, the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

IMMUNOLOGY DEVICES PANEL

December 3, 2008

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY J. ATKINSON, JR.

Official Reporter