1   The ROMA study -- the cohort study was aimed

2   at validating set sensitivities at a set specificity

3   for the cohort study of that ROMA combination, not at

4   differentiating a finer result between CA-125 alone and

5   HE4 plus CA-125 and the ROMA. There simply wasn't the

6   power there to do it.

7   DR. FUNKHOUSER: Based on your pilot data, is

8   there a statistically significant difference between

9   those two numbers?

10   DR. SKATES: Yes.

11   DR. NETTO: And that's not the ROMA formula,

12   correct?

13   DR. SKATES: It's not --

14   DR. NETTO: The bottom line --

15   DR. SKATES: No, it's not the final formula,

16   the --

17   DR. NETTO: So this is either one positive or

18   adding --

19   DR. SKATES: No, it's actually a logistic

20   regression equation. It happens not to be the exact

21   version of the ROMA formula.

22   UNIDENTIFIED SPEAKER: And that's not

23   the --

24   DR. LEVY: And do you have that calculated at

25   75 percent specificity because this is at 90/95

1   percent.

2   DR. SKATES: Yeah, that's also the

3   modification that this slide -- we didn't evaluate it

4   down at the 75 percent specificity. And --

5   DR. NETTO: What would happen if you did?

6   What would happen if you did? Would the difference

7   still be significant?

8   DR. SKATES: I don't know.

9   DR. NETTO: Did you do that analysis?

10   DR. SKATES: We did not do that analysis at

11   75 percent specificity. The point --

12   DR. NETTO: And why is that if that was your

13   aim? Why wasn't it done that way if, ultimately,

14   that's your objective in the pivotal study?

15   DR. SKATES: Right. So we were evaluating 15

16   biomarkers in the pilot studies. And what we wanted to

17   do is leave enough room for the sensitivity to increase

18   with those additional biomarkers, and, therefore, we

19   set high specificity levels with CA-125. In fact, if

20   we could put the slide on the screen, we see that there

21   are quite a number of biomarkers that we evaluated.

22   And what we wanted to do is leave maximal room for

23   determining whether or not CA-1 -- any of these

24   biomarkers by themselves or in combination added to the

25   sensitivity of CA-125. Once you get to specificities

1 down to 75 percent, there is not -- sensitivity of CA-

2 125 is quite high around 80 percent, and there's not as

3 much room. When you push the specificity up to 90/98

4 percent, there is a lot more room to see whether or not

5 any of these markers adds to that sensitivity, and we

6 want to have enough room to evaluate all of these

7 markers, not only by themselves but in combination.

8   DR. FREEDMAN: That would not be the

9 operating, usual operating range for the assay --

10   DR. SKATES: All of these were -- so CA-125

11 at 98 percent specificity is 35 units. And that's well

12 within the normal range of CA-125 assays. All of --

13   DR. FREEDMAN: But in the ACOG

14 recommendations, they have suggested higher levels like

15 200 or even 50 as a cutoff --

16   DR. SKATES: Absolutely. I agree. So that

17 would be even higher specificities if you use that in

18 the post-menopausal. I was referring to 35 in the

19 post-menopausal. In the pre-menopausal, the upper

20 limit at 98 percent in the studies that I have done

21 have been around 50 to 60. And that's still well

22 within the operating characteristics of the test that

23 CA-125 manufacturers provide.

24   DR. FREEDMAN: And the other feature about

25 your pilot studies, you had more than one assay, CA-125

1 assay --

2   DR. SKATES: That's correct. That's a detail

3 that we haven't --

4   DR. FREEDMAN: Which can cause variability,

5 as well-known --

6   DR. SKATES: Yes. Now, that variability was

7 taken into account in terms of setting -- in fact,

8 slide on screen. We actually had in the Boston study

9 the Elecsys 2010 from Roche CA-125 evaluated. That

10 used up all the serum from that study. We had to

11 impute the Architect CA-125, which is what was used in

12 the Rhode Island study.

13   And there was a separate study of 98 patients

14 which showed the high correlation between the Architect

15 and the CA-125. You can see that that correlation

16 there is about 98 percent. And we fit a linear

17 regression to that Architect CA-125 on the Elecsys 2010

18 and used that to impute the Architect values in the

19 Boston study. Slide on screen.

20   So, in fact, we used multiple imputation to

21 capture the fact that it was not 100 percent

22 correlation and that actually accommodates the fact

23 that it's not a perfect correlation there.

24   DR. FREEDMAN: I don't want to belabor the

25 point, but when you have different institutions doing

1   an assay like CA-125, there's data out there that shows

2   that you can get a variety of labels, quite a big

3   difference in labels. So one institution was excluded

4   totally, right, a large component of your samples

5   because they didn't have enough samples available?

6   DR. SKATES: Not excluded. The values were

7   imputed from that linear regression that I just showed

8   you. So they were included in terms of assessing a

9   complementarity to Architect CA-125. But the fact that

10 there's some uncertainty between the two CA-125 tests,

11 the one that was used in Boston and the one that we --

12 the Architect CA-125, is captured in the analysis of

13 those multiple markers.

14   DR. FREEDMAN: All right. Thank you.

15   DR. NETTO: We have to move on. Dr. Lichtor?

16   DR. LICHTOR: I'm trying to understand how

17 this is really going to change management of these

18 patients. I realize it's not really my field, but on

19 your Slide 54, you talk about ROMA versus RMI. Now, my

20 understanding that the Risk of Malignancy Index, is

21 that a currently practiced screening tool? And in your

22 slide you say that is equal to your imaging score,

23 which to me can depend on how fancy you are with your

24 imaging, pre-menopausal or post-menopausal, and serum

25 CA-125, which is one of your -- one of the things you

1 already assayed. So part of the question is, is serum

2 CA-125, is that normally done because I've heard

3 conflicting things. You say it is done, it's not

4 normally done. And if it is normally done, then the

5 only thing you're really adding is another biomarker.

6 So I'm sort of confused about how this is really going

7 to change the management.

8   DR. MOORE: So the RMI is currently used in

9 clinical practice. It's not used for screening. It's

10 used to assess the risk of malignancy in patients with

11 an ovarian cyst or a pelvic mass. And CA-125, as you

12 pointed out, is part of that.

13   Now, in a post-menopausal woman that has a

14 cyst or a mass, they routinely, they'll get a CA-125.

15 Where we run into variability in terms of patients

16 getting CA-125s or not, they're normally in the pre-

17 menopausal age group because for CA-125, many of the

18 benign gynecological disorders will elevate that tumor

19 marker and even many of the non-gynecological

20 disorders, for instance, endometriosis or PID, a number

21 of things can cause a false positive elevation of CA-

22 125.

23   Now, when we look at HE4 in those groups, we

24 see that HE4 is not elevated and endometriosis is not

25 elevated and PID is not elevated and pregnancy. And

1 that's why HE4 has a much larger score to it in the

2 pre-menopausal group. And so that's where HE4 really

3 adds on to CA-125 in pre-menopausal population.

4   If we look at HE4 compared to CA-125, and

5 we've published some of this data, we know that 80

6 percent of ovarian cancer patients will express CA-125.

7 Well, 20 percent won't, even though they have an

8 advanced stage cancer. And when we look at the

9 expression of HE4, we see that it actually marks

10 slightly over half of those patients. So it gives us

11 another tumor marker in those patients.

12   As well, we've shown data that we see that

13 HE4 is a much better marker for early stage disease,

14 where CA-125 classically isn't. And this is probably

15 why the ROMA test outperforms RMI because HE4 makes up

16 for those deficiencies in CA-125. And, also, the

17 imaging has a very difficult time in telling us what's

18 a cancer in a disease that's confined to the pelvis or

19 confined to a mass.

20   DR. NETTO: Thank you. Dr. Li --

21   DR. JASON: What's interesting is the way

22 you're describing it, you would think the best approach

23 would be a variant on including them all, saying if any

24 one of these is positive.

25   DR. MOORE: And it may be. Steve, you want

1   to -- Steve would like to address that question.

2   DR. NETTO: Ms. Holland?

3   DR. SKATES: I'm sorry.

4   DR. NETTO: And then --

5   MS. HOLLAND: I don't know if any of you can

6   answer my questions, but we can try it. I have ovarian

7   cancer, Stage 3C, and in, you know, the time leading up

8   to my diagnosis in my small community, the decision was

9   made to do my surgery locally, which would have been

10 great because my husband works at the local hospital

11 and I would have been treated like a queen there. And

12 in my community, the CA-125 doesn't -- it takes three

13 days to get it back, which is a little unusual now, but

14 that's the way it is in my small town. So we scheduled

15 the surgery, and the night before, my CA-125 came back

16 at 4,700. As a result of that, I then went to a

17 hospital an hour a way and had my debulking done by a

18 GYN/oncologist, which I'm very happy. Now I know after

19 the fact how important that was. I had no idea and no

20 one told me how important that was, you know, in the

21 process.

22   My concern is with the false negatives. And

23 I know how devastating this disease is. I know it

24 firsthand, and I know how poor my prognosis is. If I

25 were told that there was, say, a 10 percent chance that

1   I could have this terrible disease and, you know, I was

2   given the option of you can either stay here and be

3   comfy in your own community and have just a GYN or a

4   general surgeon do this or you can go to, you know, a

5   more major center and have a specialist do it, I would

6   certainly choose the specialist, even if my risk was

7   low. It's that choice that I'm worried about. If, you

8   know, I'm worried that the results of this test could

9   be misused by insurance companies, for example, saying,

10 oh, you tested out low-risk, so we're not going to

11 qualify you to go out -- leave your town and go have

12 this surgery somewhere else. Or would the -- could the

13 potentially local surgeons misuse it by saying, you

14 know, arguing even with a woman who makes the choice

15 like I would, saying I don't care if I'm low-risk, I

16 want the specialist doing the surgery, but would I then

17 come up against a brick wall, saying, oh, no, no, no,

18 no, you should stay here and talking me out of doing

19 what I want? Do you understand my question?

20   DR. MOORE: I understand your question 100

21 percent, and I'm in your camp on that one. I'm sorry

22 that you have ovarian cancer. It looks like you're

23 doing great. You know, you're talking about the test

24 being used in all patients with a pelvic mass,

25 essentially being used by gynecologists, and we showed

1 that worst-case scenario.

2   Right now in the U.S., 50 percent of the

3 women are not being referred on that have ovarian

4 cancer. If that test were used in that scenario that

5 you're presenting, that would be a huge improvement.

6 That would mean that more patients with ovarian cancer

7 would be coming to a gynecological oncologist where we

8 can serve. She asked a hypothetical question. And I

9 agree, it's not in --

10   DR. NETTO: But that's, I think, there is a

11 little bit of unclarity about this.

12   DR. MOORE: There is.

13   DR. NETTO: These are people that already are

14 referred to an oncologist, so the 50 percent deficit

15 will be there, regardless, unless you're --

16   DR. MOORE: Um-hum.

17   DR. NETTO: -- advertising this test as

18 initial, then it would --

19   DR. MOORE: Right.

20   DR. NETTO: -- improve the 50 percent.

21   DR. MOORE: Yeah, and we're not arguing --

22   DR. NETTO: So you keep referring to that,

23 and it's not true.

24   DR. MOORE: But we're not arguing --

25   DR. NETTO: The study only showed --

1   DR. MOORE: Yes.

2   DR. NETTO: -- that these are people who

3 already are referred, so whatever lack of sensitivity

4 in referral, it's already built in unless we want to

5 use this test in the beginning to increase and make up

6 for this 40 percent. So I --

7   DR. MOORE: But --

8   DR. NETTO: -- don't want you to keep

9 repeating that because it's not true.

10   DR. MOORE: But I agree with that --

11   MS. HOLLAND: I think -- I agree with him,

12 too in that it's just the statement of intended use

13 that is really puzzling, and the language, "Subjects

14 categorized as low-risk for ovarian cancer using the

15 ROMA value may have surgical intervention performed by

16 a non-oncology specialist." And that's, you know, a

17 quote from the intended use.

18   DR. NETTO: So you're giving now, based on

19 this test, you can argue an additional 10 percent that

20 could be sent back, so it's your original 50 percent

21 could become a 60 percent miss. So that's what she's

22 referring to.

23   DR. MOORE: Yeah.

24   DR. NETTO: You're giving probably for a

25 woman who is not as willed as Ms. Holland is, probably

1   say, "Let me stay there with my GYN, then." The other

2   issue is -- go ahead.

3   MS. HOLLAND: Well, I just want to say, you

4   know, as a patient and having spoken with many other

5   patients, we want 100 percent to go to GYN oncologists.

6   Even --

7   DR. MOORE: So do I.

8   MS. HOLLAND: With any suspicion whatsoever,

9   even 5 percent probability. That's what we aim for.

10 We don't aim for something that will send people back

11 to their local guys.

12   DR. MOORE: Well, there are benefits for

13 patients with benign disease to be left in their

14 community. There are.

15   MS. HOLLAND: You know, given the difference

16 between having maybe a little bit extra surgery for a

17 benign disease and having not the right surgery for a

18 devastating disease, you know, I'd opt for the too much

19 surgery for the benign thing to tell you the truth.

20 That would make me happier.

21   DR. NETTO: Let's --

22   DR. MOORE: And I think we're in the same

23 camp. I would love for all --

24   DR. NETTO: Let me frame the question this

25 way. So in the current status without using ROMA,

1 what's the percentage you would say you would send back

2 to the GYN because you felt this shouldn't be done by a

3 GYN oncologist --

4   DR. MOORE: Well, I think that's --

5   DR. NETTO: -- of the referrals.

6   DR. MOORE: That's a very difficult question

7 to answer, and it depends on, you know, many factors.

8 For instance, we'll have patients that say, "No, I want

9 to have my cancer surgery at M.D. Anderson or Fox Chase

10 or, you know, the referral center." And I'm not going

11 to argue with them.

12   DR. NETTO: So I think this whole argument is

13 that this could introduce now a pathway to that reverse

14 referral that -- and then worrying about, what is it,

15 40 of LMPs in pre-menopausal being missed by this test,

16 too. So we're not saying that it's the harm, but we

17 have to say how much is also missed despite the test,

18 and we have to consider this possibility of people

19 latching on this as a way to go back to the regular

20 GYN, not GYN oncologist.

21   DR. MOORE: It's not 40 percent that would

22 have a cancer go back --

23   DR. NETTO: It's 30 --

24   DR. MOORE: It's 3 percent that would have a

25 cancer --

1   DR. NETTO: So it's in the pre-menopausal,

2   it's 37, it's 6 out of 16 LMPs in the pre-menopausal

3   would have been missed by this test. So it is 37.5

4   percent. So it's almost 40 percent. All right. We

5   will have another chance to ask some more question.

6   Dr. Skates, I know you wanted to --

7   DR. MOORE: I think Dr. Skates wanted to --

8   DR. NETTO: And after that, we'll leave the

9   remaining questions to after a short break. Go ahead.

10   DR. SKATES: I was just pointing out that the

11 denominator was where the issue was in that past

12 exchange. Six out of sixteen is correct, and if we

13 could have the slide on the screen, we see that -- but

14 if you look at the denominator, 6 in the LMPs, there

15 were 6 in the pre-menopausal and 3 in the post-

16 menopausal, and these were correctly classified 9 out

17 of the 16. But if you look on the horizontal version

18 of this, then the denominator is 111 post-menopausal

19 patients and 18 pre-menopausal cancers. And that's

20 where the 3 percent and the 6 percent came from.

21   DR. NETTO: All right. Since we're running

22 behind, we'll have a five-minute break instead of 15-

23 minute break, and we'll meet again here. Should be no

24 discussion of the Panel topic during the break amongst

25 yourself or the Panel members or with any member of the

1 audience. And we'll resume in five minutes.

2   (Off the record.)

3   (On the record at 11:28 a.m.)

4   DR. NETTO: It's now 11:28, and I would like

5 to call the meeting back to order. The FDA will now

6 give their presentation on this issue. So the

7 presenters from the FDA are Dr. Reeves,

8 Dr. Kondratovich, and Dr. Becker, and you will have one

9 hour.

10   DR. REEVES: Thank you very much. Good

11 morning, Panel members, representatives of Fujirebio,

12 FDA colleagues, and members of the public. Women who

13 are presenting with symptoms and signs of a pelvic mass

14 often pose a diagnostic challenge, especially

15 concerning the distinction of benign from malignant

16 ovarian disease. For some patients, a requirement for

17 surgery becomes less necessary when establishing the

18 correct diagnosis, treating the expected disease, or

19 doing both.

20   In arranging exploratory or definitive

21 surgery when a surgery is necessary for other patients,

22 a major clinical question is whose clinical services

23 will give the best clinical outcome based on the

24 likelihood of benign versus malignant disease. Though

25 the need for oncology expertise in evaluating the

1 patient may be clear, the need for oncologist resources

2 in performing the surgery might still be an open

3 question.

4   For the proposed device under review and

5 Panel comment, the Sponsor has proposed a new intended

6 use and indications for use for which I would like to

7 highlight various portions on the following slides.

8 This first section of the intended use described the

9 device. The Risk of Ovarian Malignancy, or ROMA,

10 relies on the results from two in vitro diagnostic

11 tests, CA-125 and HE4. The device uses a specified

12 mathematical function to calculate a Predictive

13 Probability for the presence of malignant ovarian

14 disease.

15   The intended use population is specifically

16 described in the next section. The Risk of Ovarian

17 Malignancy Algorithm is for use in pre-menopausal and

18 post-menopausal women who have an adnexal mass and who

19 have already been referred to an oncologic specialist

20 and are scheduled for surgery. The intended use

21 population is meant to align with the sample population

22 from the Sponsor's study of the test's clinical

23 performance. The Predictive Probability is not used as

24 an aid in a decision to proceed to surgery nor is the

25 risk calculation utilized to make a decision on

1 referring pre- and post-menopausal women to an

2 oncologic specialist.

3   The FDA seeks the Panel's advice concerning

4 the suitability of the definition of the intended use

5 population for the test as it will be used in practice.

6   The next section of the intended use is the

7 stated answer to the question: Whose surgical skills

8 could be used? It speaks to the point that a required

9 surgery may be performed by a non-oncology specialist

10 or an oncology-referred patient even when and if a

11 surgical need remains an open question. The clinical

12 impact of the test is to help decide this treatment

13 question for patients in the specified clinical study.

14   The FDA seeks the Panel's advice concerning

15 the safety and effectiveness of the algorithm regarding

16 this clinical impact.

17   It is true in many situations that diagnostic

18 tests should be considered in the total clinical

19 context. Yet, the matter in which this should be done

20 is seldom specified. The Sponsor's indication for use

21 includes the statement that results must be interpreted

22 in conjunction with other clinical findings, in

23 accordance with standard clinical management

24 guidelines. There are published guidelines for pelvic

25 mass evaluation and treatment, but they do not speak to

1   the use of this test or indeed to the specific intended

2   use population described for this test.

3   An evaluation of the manner in which test

4   results can be safely and effectively combined with

5   other clinicopathologic data has not been carried out

6   for this Risk of Ovarian Malignancy Algorithm. Study

7   subjects arrived at the referral centers with their own

8   symptoms, physical findings, and imaging results, but

9   this information was not captured or integrated into

10 the surgical decision by the study design.

11   It is unclear to us if the test can or should

12 be used as a standalone test, absent other information,

13 in order to appropriately decide surgery by a

14 specialist or non-specialist, or can knowledgeably and

15 safely be combined with other clinical findings for the

16 intended use population by clinicians.

17   The FDA seeks the Panel's advice concerning

18 whether and how the results of this algorithm can be

19 safely and effectively combined with other information.

20   Analytical performance characteristics are an

21 important element in the use of any in vitro diagnostic

22 test. Both the CA-125 and HE4 assays, the two

23 individual components in the algorithm, are based on

24 well-established dual-antibody sandwich immunoassay

25 technologies. Each assay has been previously cleared

1 by the FDA for use in patients with established ovarian

2 cancer to aid in monitoring cancer status. As

3 background information, the package inserts for these

4 assays has been provided and the information supplied

5 to Panel members and the public.

6   One analytical feature of interest is the

7 variability in the predictive index, as calculated by

8 the algorithm, due to imprecision of the two component

9 assays. The Sponsor utilized an average estimate of

10 total imprecision for each component assay on which to

11 base imprecision of the predictive index. For CA-125,

12 a percent CV of total imprecision of 3.4 percent was

13 utilized while a value of 5.5 percent was utilized for

14 HE4. As a result of the imprecision, the predictive

15 index of the Risk of Ovarian Malignancy Algorithm has a

16 standard deviation of imprecision of 0.135 in pre-

17 menopausal women and 0.063 in post-menopausal women.

18   To visualize the effect of the imprecision of

19 the predictive index due to the imprecision of the

20 component assays, this graph illustrates scatter plots

21 of pairs of CA-125 and HE4 assay values for study

22 subjects. On the graph is also included the line --

23 cutoff corresponding to the specificity of 75 percent

24 and the upper and lower limits around the line due to

25 random imprecision. Subjects above the line in each

1 graph are classified as high-risk, while subjects below

2 the line are classified as low-risk. Some subjects are

3 near the line. In pre-menopausal women, 20 percent of

4 subjects were within the limits of imprecision, while

5 in post-menopausal women, approximately 4 percent of

6 subjects were within the limits of imprecision.

7 Turning now to the pivotal study design,

8 utilizing 14 different gynecologic oncology care

9 centers throughout the United States, female subjects,

10 age 18 years or older, who were referred to these

11 centers with an image-documented pelvic mass and

12 scheduled for surgery, were included. Subjects

13 underwent laparoscopic surgery or laparotomy. Patients

14 were excluded if they received treatment for any

15 malignancy, cytotoxic chemotherapy treatment, were

16 absent ovaries due to surgical removal, or were

17 pregnant.

18 Serum was removed for testing the HE4 and CA-

19 125 assays at separate testing sites, but patient

20 management and histopathological diagnosis occurred at

21 the local oncology sites. Final histopathology was

22 reviewed multiple times, first locally by pathologist

23 and then centrally reviewed. Final review of clinical

24 histological information was performed by two

25 gynecologic oncologists. Decisions regarding patient

1 management remained local and were made blinded to

2 device results.

3   Subsequent to the realization that menopausal

4 status was a statistically significant factor in

5 predicting the cancer probability, the Sponsor

6 developed a two-equation classifier. These model

7 equations were evaluated in the final validation study

8 and are described in the additional analysis. The

9 additional analysis shows Predictive Probability cutoff

10 values after protocol analysis in the validation study

11 indicated that 75 percent specificity would yield a

12 sensitivity above 80 percent at it's lower 95 percent

13 confidence level.

14   Redetermination of the menopausal status of

15 54 women was undertaken after initial submission to the

16 FDA, utilizing additional rules to assign menopausal

17 status according to the patient's age, prior surgical

18 history, or absence of a known date for the last

19 menstrual period, and ovarian function testing based on

20 the measurement of follicle stimulating hormone in

21 serum using the Abbott Architect FSH assay, and a -- 22

22 milli international units per ML. The redetermination

23 reclassified as pre-menopausal 39 women who were

24 originally considered post-menopausal. It also

25 determined the menopausal status of 7 women who were

1 previously indeterminate, enabling their inclusion in

2 the additional analysis.

3   We ask your comment on the reliability of

4 general methods of menopausal status determination and

5 if specific instructions are needed to ensure safe and

6 effective use of the ROMA algorithm. Thank you very

7 much for your attention. I would like to turn over our

8 discussion to Dr. Marina Kondratovich, who will discuss

9 results and statistical analysis.

10   DR. KONDRATOVICH: Good morning. I will

11 start my presentation with introduction. Then we will

12 consider performance of ROMA test as a standalone test;

13 then performance of the ROMA test versus CA-125 alone

14 versus HE4 alone for the patient with LMP or epithelial

15 ovarian cancer; then also for the patient with Stages 1

16 and 2 of epithelial ovarian cancer. And then I will

17 conclude with summary.

18   Let me start introduction with remark about

19 intended use population subject in the clinical study.

20 Consider the subject was scheduled for surgery, this

21 table present all subject who are scheduled for

22 surgery. These subjects can be divided into two

23 groups. One group is the subjects who were assessed by

24 physician using pre-surgical available information like

25 malignant, high-risk subjects. Probably all these

1 subjects were referred to oncology centers, so these

2 subjects part of the clinical study. Second group is

3 the subjects who were assessed by physician using pre-

4 surgical available information like nonmalignant, low-

5 risk subjects.

6   In reality, this subject is also divided into

7 two groups. One group is the subjects who were

8 operated in oncology centers. And this group of

9 subjects is really included in the clinical study. But

10 this group of subjects, who were operated in places

11 other than oncology centers, were not included in the

12 clinical study. So we really don't know performance of

13 the ROMA test for this group of subjects. This is the

14 reason that intended use really cited in that way, that

15 patients who have already been referred to oncology

16 specialist and who are scheduled for surgery, exactly

17 this group and half of this -- not half -- some -- part

18 of the nonmalignant, low-risk, how it was assessed by

19 physician.

20   It is assumed that the ROMA test will be used

21 in conjunction with other clinical findings in patient

22 with pelvic mass who were referred to oncology center

23 and scheduled for surgery. However, no ancillary pre-

24 surgical information was provided for evaluation

25 besides or in combination with test results.

1 Therefore, performance of the ROMA test can be

2 evaluated only as a standalone test. And in my

3 presentation, you will see performance of the ROMA test

4 as a standalone test. But I would like to emphasize

5 that evaluation of a medical test as a standalone test

6 does not provide information -- medical test improve

7 patient care beyond what is possible with available

8 pre-surgical information alone.

9   The algorithm that combines CA-125 and HE4

10 concentration was developed using a training set. You

11 already saw this formula for pre-menopausal and post-

12 menopausal women, and the weights are different. ROMA

13 results here for percent units and value from 0 to 100.

14   Cutoffs for defining low risk and high risk

15 were calculated by the sponsor based on a pre-specified

16 level of specificity of 75 percent separately for the

17 pre-menopausal and post-menopausal subject using the

18 validation data set. In order to obtain unbiased

19 estimate of sensitivity and specificity, the cutoffs

20 for the pre-menopausal and postmenopausal subject

21 should be the estimate of the 75th percentile of

22 corresponding sets of ROMA values for the benign

23 subject.

24   But variability is larger and the appropriate

25 bootstrap can be used. So please note that in all

1 calculation of confidence interval in this

2 presentation, we do not take into the account the

3 increase in variability due to selection of the cutoff

4 in the validation study.

5   Let us consider the performance of the ROMA

6 test as a standalone test. For the pre-menopausal

7 subject, in the study, in the validation data set,

8 there were 234 pre-menopausal subjects. Among them,

9 there were 200 subjects with pathology results benign

10 and 34 subjects with pathology results LMP or

11 epithelial ovarian cancer.

12   This graph presents ROC curve for the pre-

13 menopausal subjects benign versus LMP or epithelial

14 ovarian cancer. It was Sponsor's decision to select

15 particular level of specificity, 75 percent, so this

16 line presents a specificity of 75 percent, what was

17 selected by the Sponsor. Estimation of cutoff for the

18 ROMA test, we need to use value of the ROMA test of 200

19 benign subjects. And when we use ROMA values of 200

20 benign subjects, estimate of 75 percentile, 13.4

21 percent.

22   So using this cutoff, the data of the pre-

23 menopausal for 234 subjects, the data can be presented

24 by this table, benign and LMP or epithelial ovarian

25 cancer. From this table, we can evaluate sensitivity,

1   specificity, positive and negative predictive value.

2   Sensitivity is 76.5 percent, with low-bound 60.0

3   percent. Specificity, 75.0 percent. Positive

4   predictive value is 34.2 percent, and negative

5   predictive value, 94.9 percent, with low-bound 91.6

6   percent. In this study, percent of subjects with low

7   risk was 67.5 percent, a negative predictive value,

8   94.9 percent.

9   What does this mean? It means that among 100

10   pre-menopausal subjects who already were referred to

11   oncology specialists but they were defined by the ROMA

12   test like low-risk subjects, approximately five

13   subjects have LMP or epithelial ovarian cancer.

14   This table presents more detailed information

15   about sensitivity of the ROMA test for the pre-

16   menopausal subjects. Among malignant cases missed by

17   the ROMA test, 75 percent, 6 out of 8, were LMP. And,

18   also, we see more detailed information for particular

19   category of LMP or epithelial ovarian cancer.

20   Sensitivity of ROMA test for LMP was 62.5 percent using

21   this column. For epithelial ovarian cancer, Stage 1

22   and 2, sensitivity was 85.7 percent, and for epithelial

23   ovarian cancer, Stage 3 and 4, sensitivity was 100

24   percent. Sensitivity what you saw on the previous

25   slide, 76.5. It's really average over all these

1 categories.

2 Consider post-menopausal subjects. In the

3 study, there were 270 post-menopausal subjects. Among

4 them, it was 151 subjects with pathology results benign

5 and 119 subjects with pathology results LMP or

6 epithelial ovarian cancer. This graph presents ROC

7 curve for the ROMA values for the post-menopausal

8 subject. This is level of specificity 75 percent and

9 this is the cutoff for ROMA test, which was based on

10 the specificity of 75 percent. Using ROMA values of

11 benign subject, 151, benign subject, we see that the

12 estimate of 75th percentile was 27.7 percent and this

13 cutoff is used in the post-menopausal subjects.

14 So this table presents the data of 270 post-

15 menopausal and performance of the ROMA test for this

16 subject. Sensitivity is 92.4 with low-bound 86.3

17 percent. Specificity, 74.8 percent. Positive

18 predictive value, 73.3 percent and negative predictive

19 value, 92.6 percent, with low-bound 87.3 percent.

20 Percent of subjects with low-risk among post-menopausal

21 subjects was 45.2 percent. A negative predictive value

22 for the subjects who have low-risk according to the

23 ROMA test was 92.6 percent. It means that among 100

24 post-menopausal subjects who already were referred to

25 oncology specialists and who have low-risk by the ROMA

1 test, approximately 7 subjects has LMP or epithelial

2 ovarian cancer.

3   This table presents more detailed information

4 about sensitivity. We see that among malignant cases

5 missed by the ROMA test, 33 percent, 3 out of 9, were

6 LMP cases. And this table present more detailed

7 information for particular category, performance of the

8 ROMA test. For the LMP cases, 57.1 percent, for Stage

9 1 and 2 epithelial ovarian cancer, 86.2 percent, and

10 for Stage 3 and 4, 98.8 percent. Sensitivity at 92.4

11 percent, it's really average over all these categories.

12   The Sponsor presented combination of the pre-

13 menopausal and post-menopausal subjects, where you

14 consider ROMA as qualitative test. So pre-menopausal

15 subjects can be described by this table. Post-

16 menopausals can be described by this table. ROMA test

17 is qualitative test, so provide results low-risk and

18 high-risk. But please pay attention that, of course,

19 there are different cutoffs. What is the meaning of

20 low-risk and high-risk for the pre- and post-menopausal

21 subject?

22   So we combined data, and we're using this

23 table for combined data. We see that sensitivity was

24 88.9 percent, with low-bound 82.9 percent. Negative

25 predictive value was 93.9 percent, with low-bound 90.9

1 percent. So you see that it was claimed that

2 sensitivity for the combined data was 88.9 percent and

3 the three confidence intervals, more than 80.

4   But I would like emphasize that clinical

5 interpretation of the performance of the ROMA test for

6 the data combined in such a way depends on the

7 proportion of pre-menopausal and post-menopausal

8 patients in the study. So we really need to make

9 careful interpretation of this -- formal combination.

10 For example, consider sensitivity. Pre-menopausal

11 subject has sensitivity 76.5 percent, post-menopausal

12 subject 92.4. When we combine, we attain 88.9. But I

13 would like emphasize that sensitivities of the ROMA

14 test for the pre-menopausal and post-menopausal subject

15 were different.

16   In the combined datasets, there were 153

17 subjects with LMP or epithelial ovarian cancer. And

18 among this 153 subjects, 34 subjects were from pre-

19 menopausal and 119 from post-menopausal group. So

20 post-menopausal comprised 78 percent of the all

21 malignant cases. When we calculated sensitivity of the

22 combined data, in reality, what we're doing, we're

23 calculating linear combination of the sensitivity of

24 the pre-menopausal subjects, sensitivity of the post-

25 menopausal subjects with weight, and these weights

1 correspond to the proportional, the pre- and post-

2 menopausal subjects among all malignant. But every

3 particular woman belongs only to one group, pre-

4 menopausal or post-menopausal, so this linear

5 combination presents some kind of sensitivity. It's

6 even difficult to tell what kind of subject.

7   So we really need to pay attention that

8 sensitivity for the pre-menopausal was only 76, around

9 76 percent, and it was different from the post-

10 menopausal.

11   This table presents combining of the ROMA

12 performance when we take into the account spectrum of

13 disease. We see that performance of the ROMA test for

14 the LMP almost the same for the pre-menopausal and

15 post-menopausal subject. Indeed, for example, the ROMA

16 test has sensitivity 62.5 percent and sensitivity for

17 the post-menopausal for the same category, 57.1.

18 Similar for the Stage 1 and 2. For pre-menopausal,

19 ROMA has sensitivity 85.7 percent, and for post-

20 menopausal, 86.2 percent. For Stage 3 and 4, 198.8.

21   So we can combine data for each particular

22 category. We saw different sensitivity for pre-

23 menopausal and post-menopausal subject because there

24 are different proportions of these categories for pre-

25 menopausal and post-menopausal subject. For example,

1   LMP among pre-menopausal comprised 50 percent, while in

2   post-menopausal subject, it was only 6 percent. Stage

3   3 and 4 for pre-menopausal comprised 28 percent and for

4   post-menopausal is 70 percent. So when we combine data

5   for each particular category, then we see that for LMP

6   sensitivity, around 61 percent, for Stage 1 and 2

7   epithelial ovarian cancer, around 86 percent, and for

8   Stage 3 and 4, around 99 percent. And this is the

9   corresponding low-bound of 95 confidence interval.

10   Let us consider performance of the ROMA test

11 versus CA-125 alone versus HE4 alone for the patient

12 with LMP and epithelial ovarian cancer. For pre-

13 menopausal subject, this graph presents ROC curve for

14 the ROMA test. This is orange line. For the CA-125

15 alone, blue line, and for HE3 [sic] alone, green line.

16 So these three ROC curves, the Sponsor selected a

17 cutoff based on a specified level of specificity, 75

18 percent. I would like emphasize that in the training

19 set, it looks like the Sponsor looked at the high level

20 of specificity, like 95 -- 90 percent. Yes, probably

21 in this level of specificity there are some

22 contributions from HE4. But the level of sensitivity

23 here is really very low, probably clinically

24 unacceptable. So consider only the cutoff which was

25 proposed by the Sponsor, 75 percent.

1   So when we selected this level of

2 specificity, we right now would like to know what is

3 the cutoff for the particular ROC curve. So every

4 subject -- like, we can see the only benign subject,

5 and every subject has three values, ROMA value, CA-125

6 alone, and HE4 alone. So when I'm using ROMA values of

7 the benign subjects, 75th percentile, 13.4. If I using

8 CA-125 values of the benign subjects, cutoff 60.4

9 international units per milliliter. If I use HE4

10 alone, 75th percentile and 63.6 picomole so right now,

11 we have that this level of specificity and these are

12 particular levels of sensitivity. So these values of

13 level of sensitivity are when level of specificity, 75

14 percent. So ROMA has 76.5 percent; in CA-125 alone,

15 79.4 percent; HE4 alone, 73.5 percent.

16   So let us investigate. Do we have some

17 improvement, ROMA test compared to CA-125 alone? We

18 have 34 subjects. Among them, ROMA test have high-risk

19 for 26 subjects. And CA-125 have positive results with

20 the cutoff which corresponds the same level of

21 sensitivity, 75 percent, have 27 subjects. So we see

22 even some small decrease in sensitivity, 1 out of 34,

23 minus 2.9 percent. Confidence interval, of course,

24 relatively large, zero belongs to this confidence

25 interval.

1   This scatter plot presents the same

2   information only a little different way. This is the

3   benign subject, and the red is LMP or epithelial

4   ovarian cancer. This line presents cutoff line for the

5   ROMA test with specificity of 75 percent. So all

6   values for ROMA test here is negative and all values

7   for ROMA test here is positive. So sensitivity of the

8   ROMA test at 76.5 percent. This line presents cutoff

9   for the CA-125 alone with specificity 75 percent.

10   These results are negative for CA-125 alone, these

11   results are positive. So sensitivity is 79.5 percent.

12   So the data of the clinical study did not

13   demonstrate that there was statistically significant

14   contribution of the HE4 test beyond the CA-125 in the

15   combination ROMA for the pre-menopausal woman. Indeed,

16   for the same level of specificity of 75 percent,

17   sensitivity of CA-125 alone was 79.5 percent, and for

18   combination, 76.5 percent.

19   Consider post-menopausal subject. This graph

20   presents three ROC curves for the post-menopausal

21   subject, orange for the ROMA test, blue for the CA-125

22   alone, and green one for the HE4 alone. You can see,

23   like, for example, for the high level of specificity,

24   we did not see any difference between curves.

25   But Sponsor suggested to consider level of

1   specificity of 75 percent, so consider this level.

2   This line presents level of specificity of 75 percent.

3   Using benign subject of ROMA value, CA-125 values, HE4

4   values, we can calculate 75th percentile, and we see

5   that the ROMA cutoff, 27.7 percent. CA-125 alone, 30.0

6   international units per milliliter, and HE4 alone,

7   102.7 picomole. So this is a particular cutoff on the

8   ROC curve.

9   Using this cutoff, we can calculate what are

10 the levels of sensitivity. This level of sensitivity

11 for the level of specificity of 75. So estimate of

12 sensitivity for the ROMA, 92.4 percent, for CA-125

13 alone, 90.8 percent. In HE4 alone, it's only 84.0

14 percent. So let us investigate if there are some

15 statistically significant improvement in sensitivity of

16 ROMA test compared to CA-125 alone.

17   In the studies, there were 119 subjects with

18 LMP or epithelial ovarian cancer, and the ROMA test put

19 110 subjects as subjects with high-risk. In the CA-125

20 alone put 108 subjects. So we have some kind of

21 improvement by two subjects. So we observe some

22 improvement, 1.7 percent, 2 out of 119, but confidence

23 interval included zero. It means that we can explain

24 this, observe small improvement by chance alone.

25   Similar scatter plot presents similar

1 information in little different way. So here is cutoff

2 for the ROMA test, which this cutoff line corresponds

3 75 percent specificity and sensitivity of the ROMA

4 test, 92.4 percent. Values of the ROMA test here is

5 negative and here are positive. This line presents CA-

6 125 alone. This value for the CA-125 alone will be

7 negative and here will be positive. Sensitivity is

8 90.8 percent.

9   So the data of the clinical study did not

10 demonstrate that there was a statistically significant

11 contribution of HE4 test beyond the CA-125 in the

12 combination ROMA for the post-menopausal woman. For

13 the same level of specificity of 75, sensitivity of CA-

14 125 alone was 90.8 percent, sensitivity of combination

15 of CA-125 and HE4 was 92.4 percent, and increase in

16 sensitivity was not statistically significant.

17   Let us consider performance of the ROMA test

18 versus CA-125 alone versus HE4 alone for the patient

19 with Stages 1 and 2 of epithelial ovarian cancer. This

20 table presents detailed information for sensitivity for

21 the pre-menopausal subject and post-menopausal subject.

22 So this for the category LMP, this for category

23 epithelial ovarian cancer, Stage 1, 2, and this Stage 3

24 and 4.

25   And this column presents sensitivity average

1 over all these categories. This sensitivity average

2 all these categories, and similar for the post-

3 menopausal subject. In the studies, there were seven

4 subject from pre-menopausal group with Stage 1 and 2.

5 CA-125 detected 4 out of 7, and ROMA test detected 6

6 out of 7. So we see some improvement, two subjects.

7 But, of course, with this small sample size, this

8 improvement was not statistically significant, even if

9 we observe some improvement.

10 Among post-menopausal subjects, there were 29

11 subjects with Stage 1 and 2, and CA-125 put positive

12 24, in the ROMA, 25. So we have only additional one

13 subject. It's not statistically significant. But let

14 us combine this data and this data. Maybe we can reach

15 statistical significance.

16 So we have combined 36 patients with Stage 1

17 and 2 of epithelial ovarian cancer. We have 36

18 subjects. And for combined data, ROMA was high-risk,

19 has 31 subjects, and CA-125 alone, 28. So we have

20 three additional subjects from the ROMA test. This 3

21 out of 36 present 8.3 percent improvement, and

22 sensitivity by the confidence interval included zero.

23 It means that there was no statistically significant

24 improvement in sensitivity of the combination of CA-125

25 and HE4 for the pre-menopausal and post-menopausal

1   patients of Stage 1 and 2 with this sample size.

2   This table presents -- for comparison

3   information ROMA versus RMI versus CA-125 alone. These

4   first two lines present information which you already

5   saw in the Sponsor's presentation. For example, for

6   the all stages, epithelial ovarian cancer, ROMA has

7   sensitivity 93.8. And please pay attention, the ROMA

8   is the combination of CA-125 and HE4. RMI is the

9   combination of CA-125 and imaging and, according to

10   Sponsor calculation sensitivity, was the same level of

11   specificity, 75 percent, was 85.0 percent. But from

12   previous analysis, we saw that CA-125 alone has

13   sensitivity, 92.3 percent with specificity, 75 percent.

14   So it's really very unusual behavior of the RMI index

15   because RMI index included additional information from

16   imaging. So one can expect that at least level of

17   sensitivity should be not worse, the same or even maybe

18   better.

19   In here, we see some decrease, 7 percent.

20   Similar situation for the sensitivity for epithelial

21   ovarian cancer Stage 1 and 2. ROMA test has 86.1

22   percent. RMI, according to the Sponsor calculation,

23   66.0 percent. But CA-125 alone has 77.8 percent. So

24   it's very unusual behavior of this index, which

25   included information from imaging and, nevertheless,

1 there a loss in sensitivity around 11 percent.

2   In summary, clinical study included only

3 subject who were referred to oncology specialists and

4 who were scheduled for surgery. No risk assessment

5 based on pre-surgical information by physician was

6 provided. Therefore, ROMA test can be evaluated only

7 as a standalone test.

8   Performance of the ROMA test as a standalone

9 test summary presented here. Pre-menopausal subject

10 sensitivity and NPV, post-menopausal subject

11 sensitivity and NPV, and low-bound of 95 confidence

12 interval. No statistically significant contribution of

13 HE4 in the ROMA test versus CA-125 alone for the LMP or

14 epithelial ovarian cancer cases and no statistically

15 significant contribution of HE4 in the ROMA test versus

16 CA-125 alone for the Stage 1 and 2 of epithelial

17 ovarian cancer. Thank you very much for your

18 attention. Dr. Robert Becker will present about

19 clinical issues.

20   DR. NETTO: Thank you.

21   DR. BECKER: So I need to figure out how to

22 get to my presentation. Thank you very much. You have

23 heard many reasons today why improved laboratory

24 testing is needed to help distinguish ovarian cancer

25 from benign pelvic or adnexal pathology. In essence,

1 the diagnostic challenges fit together with the

2 treatment challenges as factors affecting the potential

3 for a cure, long-term disease management, and

4 palliation are better defined.

5   To use any diagnostic test safely and

6 effectively, one should understand its performance

7 characteristics within the intended use population, the

8 test's sensitivity and specificity for disease, and

9 given information about disease prevalence, the

10 positive and negative predictive values of the test

11 should be exploited with knowledge about the impact of

12 further diagnostic and treatment efforts.

13   A telling example comes from studies of CA-

14 125 as an ovarian cancer marker in the adult female

15 general population. Despite a clear association

16 between the marker and the disease, the low prevalence

17 of ovarian cancer in the general population plus the

18 cost and morbidity associated with definitive follow-up

19 seriously limits the value of screening with CA-125

20 alone. Potentially useful strategies for improving

21 performance include adding informative tumor markers,

22 changing the intended use population, or both.

23   Both strategies were employed in designing

24 the ROMA test. HE4 was added for use along with CA-

25 125. The combination test was designed to deliver 75

1 percent specificity in ovarian cancer detection, with

2 other performance characteristics then measured from

3 the pivotal study. You have heard different

4 conclusions today as to the significance of the HE4

5 contribution in the ROMA model. In results for the

6 test used at the prescribed cutoff for the pivotal

7 study population, FDA has not found evidence for

8 independent contribution by HE4 with the size of the

9 study as performed.

10   The patients in Fujirebio's study were, by

11 design, not a general screening population, having been

12 chosen in part to increase the prevalence of disease.

13 They were considered representative of women going to

14 surgery after referral for pelvic mass to one of the 14

15 participating gynecologic oncology institutions. This

16 specification of the intended use population is

17 fundamental and deserves further comment.

18   The patient group at the bottom of this slide

19 is the intended use population. Of course, these

20 patients, providers, and decisions stand in a larger

21 context. They result from a chain of patient

22 presentations and possibly referrals in the community

23 setting. An example of patients not included in the

24 study is women who, though perhaps symptomatic, had no

25 pelvic mass found or who had a mass that was worked up

1 and treated by their community gynecologist. These

2 groups of patients, those who are referred and treated

3 at oncology centers and those who are evaluated and

4 treated in their community, are distinct for reasons I

5 will give in the next slide. And the test performance

6 is properly described in terms of the referred group of

7 patients.

8   There were other circumstances for

9 presentation and treatment of patients, too, and, of

10 course, there was a large number of women who are free

11 of both symptoms and signs of ovarian cancer. None of

12 these additional groups of patients are included in the

13 assessment of ROMA performance. The potential impact

14 described with use of the ROMA test is to enable

15 community-based treatment of some patients who were

16 referred to the oncology setting.

17   There are two reasons why assertions about

18 test performance are best confined to the test's use in

19 patients like the ones studied. One reason is the

20 likelihood that the prevalence of diseases, whether

21 malignant or benign, varies substantially across

22 studied and unstudied patient groups. As discussed

23 already, varying disease prevalence affects positive

24 and negative predictive values. A second reason is

25 that the spectrum of disease varies across the

1 populations. Therefore, estimates of sensitivity and

2 specificity in one population may not be valid for

3 another population.

4   Variation in the stage -- distribution of

5 disease across populations is one readily understood

6 source for variation in sensitivity and specificity.

7 However, there are also instances in which patients

8 with similar stage are differently managed, that is,

9 referred or not. We do not know the factors that cause

10 these differences, which lead to sub-optimal treatment

11 results for some patients. The performance of the test

12 in the unstudied populations can be assessed with

13 certainty only by studying the test in those

14 populations.

15   With these considerations about the intended

16 use in mind, a question posed for discussion today

17 concerns the congruence of the studied population with

18 the intended use population and suitable labeling for

19 the test in light of this.

20   The choice of the population enrolled in

21 Fujirebio's study had two important useful effects.

22 One was that a strong clinical truth, that is, the

23 surgical and pathological findings, was assured for

24 virtually all patients enrolled. This is a much

25 stronger study design than one that relies on soft

1 diagnoses for truth or that fails to assess a

2 definitive diagnostic truth for all patients.

3   The second important effect was that

4 Fujirebio set conditions where the prevalence of cancer

5 was increased many fold. With a 75 percent specificity

6 that Fujirebio designed into their test through the

7 ROMA cutoff selection, the measured sensitivity was

8 about 89 percent for all patients combined with

9 positive predictive value of about 60 percent and

10 negative predictive value of about 94 percent.

11   Figures for sensitivity varied substantially

12 between the pre-menopausal and post-menopausal patient

13 subsets, with the test detecting 76 percent of the

14 malignant disease among pre-menopausal women and 92

15 percent of the malignant disease among post-menopausal

16 women. Due partly to the lower prevalence of malignant

17 disease among the pre-menopausal women, the negative

18 predictive values were similar for the two patient

19 subsets. Still, about 5 percent of the pre-menopausal

20 women who are ROMA negative and about 7 percent of the

21 post-menopausal who are ROMA negative have malignant

22 disease.

23   FDA's questions to the Panel especially

24 concern whether the figures for detecting malignant

25 disease and for concluding that individuals who test

1 negative are free of malignant disease are consistent

2 with safe use of the test to identify patients who do

3 not need cancer surgery. That is, does the test have

4 sufficient sensitivity and negative predictive value

5 for safe use in the pre-menopausal and post-menopausal

6 intended use populations?

7   It's important to consider test-driven

8 departure from current patterns of practice at oncology

9 centers in assessing safe use of the test. Let us

10 ignore patients beyond the intended use population and

11 consider just the intended use setting. If all

12 oncology-referred patients currently undergo oncology

13 surgery, then any difference between the test's NPV and

14 the ideal value of 1.0 represents patients for whom

15 false negative results might pose a new risk for sub-

16 optimal surgery. Of course, some oncology-referred

17 patients might currently be sent for a non-oncology

18 surgery at the same institution or for no surgery at

19 all. For these patients, pre-operative detection of

20 some who need oncology surgery would be beneficial.

21 But we have no data to establish the new test's value

22 in this regard since such patients were not studied.

23 We do not have information on how well the test works

24 to identify patients who need oncology surgery but

25 currently do not receive it.

1   I'll speak now about two ways in which

2   practical impact of the ROMA test might be better

3   understood. One is to understand ROMA performance in

4   the context of other clinicopathologic information; for

5   example, by studying the interaction of ROMA with

6   covariates in the statistical analysis. However, the

7   Sponsor's statistical analysis plan was confined to

8   examining the standalone performance of the test, that

9   is, test performance without reference to other

10 clinicopathological variance.

11   Of course, integrated evaluation of all

12 patient data in context is a strong clinical principle.

13 This rests partly on the expectation that added value

14 for patient management comes from correlating results.

15 However, there is no guarantee that adding a new test

16 sharpens the diagnostic edge. Adding one more test

17 might simply echo or contradict rather than enhance

18 information available from other sources.

19   An example of such unanticipated effects is

20 in the Sponsor's own dataset from their ad hoc

21 comparison of results from ROMA and the, and the

22 British Risk of Malignancy Index, or RMI. The RMI

23 method, which adds imaging information to menopausal

24 status and CA-125 surprisingly performed substantially

25 worse in Sponsor's hands than did CA-125 alone.

1 Lacking information about symptoms and signs in the

2 Sponsor's pivotal study population, FDA is not able to

3 assess the likely performance characteristics for

4 Sponsor's test used in conjunction with other tests.

5 One of FDA's questions to the Panel asks for

6 your assessment about how the new test might be

7 knowledgeably used in conjunction with other tests. Or

8 if you, too, cannot draw conclusions, how might one

9 practicably obtain such knowledge about interactions.

10 Another way to assess the practical impact of

11 the ROMA test is to examine ways of mitigating the

12 effect of miscalls. There are at least two plausible

13 paths to such mitigation. One is if the ill effect

14 from misdiagnosis is small especially compared to the

15 benefit from correct diagnosis. From the pivotal

16 study, false negative ROMA results appear to occur more

17 frequently in cases with tumors of low-malignant-

18 potential or with low-stage ovarian cancer. Such cases

19 appear to be concentrated among pre-menopausal

20 patients. The lowest false negative call rates appear

21 to occur among patients with high stage disease.

22 Now, the potential cost from false negative

23 to LMP tumors or low-stage cancers might be the need

24 for secondary surgical procedures in order to complete

25 the diagnosis and staging efforts. Though LMP disease

1 might then be conservatively managed without further

2 ill effect, there remains a concern about ensuring

3 optimal management of invasive disease that presented

4 at a low stage. The potential cost from false

5 negatives for high-stage disease is sub-optimal

6 palliation.

7   All of these considerations relate to

8 patients who were originally scheduled for cancer

9 surgery rather than non-oncology procedures so that any

10 false negative, whether missing high or low stage

11 disease, poses a risk for harm.

12   An FDA question asks you whether the harm is

13 significantly different for relatively common miscalls

14 among LMP or low-stage patients than it is for less

15 common miscalls among high-stage cancer patients. This

16 question is posed to help us assess the relative risks

17 and benefits from the test as a function of the kind of

18 cases that were called correctly or incorrectly.

19   A second path to mitigating the effect of

20 false negative test results arises if the surgery can

21 be intraoperatively converted to a procedure for cancer

22 staging and cytoreduction. This requires the rapid

23 availability of appropriate personnel and physical

24 resources, and it assumes that the earlier part of the

25 operation was without detriment to the patient. Such

1 detriment might arise, for example, through rupture of

2 a malignant cyst.

3   A question from FDA asks the Panel to

4 consider the practicality and benefit of an

5 intraoperative conversion approach to mitigating the

6 effect of false negative test results in the intended

7 use population.

8   The final area in which FDA seeks the Panel's

9 advice concerns the determination of menopausal status

10 for women who will receive the test. ROMA uses a

11 substantially different combination of CA-125 and HE4

12 results to classify pre-menopausal patients than it

13 does to classify post-menopausal patients. The FDA

14 review team is not aware of a well-standardized and

15 widely accepted manner of determining menopausal

16 status. You heard details from Dr. Reeves earlier

17 about changes in the method for assessing menopausal

18 status during the ROMA study resulting in re-assignment

19 of 39 patients from post-menopausal to pre-menopausal

20 status. Now, this did not cause a substantial shift in

21 the performance characteristics for the test as

22 measured in the ROMA study. FDA is not sure, however,

23 what might be the effect of applying various menopausal

24 criteria when the test is widely used in daily

25 practice. We ask Panel's opinion about methods for

1 assessing menopausal and about any need for

2 standardization of such methods when used as part of

3 ROMA.

4   FDA poses six questions for Panel to

5 consider. The most important question, surely, is the

6 second one concerning safety and effectiveness of the

7 test as it will be deployed. FDA believes that the

8 other five questions will bear substantially on your

9 consideration of the overriding question of safety and

10 effectiveness. Thank you very much.

11   DR. NETTO: Thank you. I'd like to thank the

12 FDA speakers for their presentations. And since we're

13 late already for lunch, we'll hold on on the questions

14 until after lunch. We will have shorter than usual

15 lunch, so we should be back at 1:20.

16 (Whereupon, a lunch recess was taken.)

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1   A F T E R N O O N   S E S S I O N

2   DR. NETTO: I would like to call the meeting

3   back to order, please. Okay. It's a little over 1:20,

4   and I would like to call the meeting back to order.

5   UNIDENTIFIED SPEAKER: You need a gavel. You

6   need a gavel.

7   DR. NETTO: Before we begin the Panel

8   deliberation since we -- yeah, okay. I'll wait while

9   the Panel members make it back. We will first start

10   with any Panel member question toward the FDA, and you

11   guys will get a chance to comment on that, too. But

12   let me wait until the Panel member makes it completely

13   back. I think we're -- would it be okay to proceed

14   without the two, two members? We only have two

15   missing. We're going to be okay --

16   UNIDENTIFIED SPEAKER: I mean, go ahead if

17   that's -- you want to.

18   DR. NETTO: So we'll go ahead and proceed.

19   Dr. Ozols will start.

20   DR. OZOLS: Yeah, I would like to ask the FDA

21   if they could explain how their statistical analysis --

22   why it is, which I interpreted it to suggest that the

23   CA-125 is just as good as any other -- good as the ROMA

24   test and as far as in the performance in this

25   population. How does your analysis differ from the

1 Sponsor's analysis suggesting the ROMA was better than

2 CA-125 and HE4? Why is there a difference in

3 interpretation?

4   DR. NETTO: Dr. Kondratovich, would you like

5 to --

6   DR. KONDRATOVICH: Well, first, my

7 understanding is that the Sponsor saw some contribution

8 from HE4 in the training set. And also, my

9 understanding that the levels of specificity were not

10 75 percent but much higher. So on a ROC curve, it's

11 probably with relatively low levels of sensitivity. At

12 least in the validation dataset with cutoff 75 percent,

13 we did not see any improvement.

14   DR. OZOLS: So it's the cutoff that

15 probably --

16   DR. KONDRATOVICH: It's difficult to tell

17 because -- maybe populations were a little different in

18 the training set. There are a lot of reasons why we

19 see different performance in the training set in

20 validation. But I would like emphasize that validation

21 set performance is the most important, not the

22 training.

23   DR. OZOLS: Um-hum.

24   UNIDENTIFIED SPEAKER: Since the --

25   DR. NETTO: Anybody from the Sponsors would

1 like to address?

2   DR. KONDRATOVICH: Yes, maybe would like to

3 explain more?

4   DR. NETTO: Thank you.

5   DR. ALLARD: I'm going to ask Dr. Skates to

6 comment as well, but I just wanted to preface his

7 remarks with just a couple of remarks to explain to you

8 how we arrived here and why HE4 in fact contributes

9 here. First thing to note I think that's very

10 important is that we're comparing to CA-125, but, of

11 course, CA-125 has never been cleared or approved by

12 FDA for this purpose. So there is no comparison there

13 in terms of a commercial available test.

14   And I just want to emphasize that HE4 was

15 selected not just based on the improvement and

16 sensitivity at fixed specificities. That was a very

17 important component, and I want Dr. Skates to mention

18 that, to emphasize that. But we also noted CA-125 has

19 two very clear flaws that I think everyone is very

20 aware of, and it's been known for well over 25 years

21 since Dr. Knapp first published the first paper on CA-

22 125 back in 1981, and that is that it's elevated

23 nonspecifically in a number of nonmalignant diseases,

24 and of course that is has low sensitivity in Stage 1

25 and 2 diseases. And I won't go through all the data,

1 but I think you've seen it this morning that HE4 does

2 address both of those limitations. It is more

3 specific, particularly in pre-menopausal women, and it

4 is also more sensitive in Stage 1, 2 disease.

5   And if I could just have the slide on, I just

6 want to show you real briefly one of the important

7 distinctions -- actually, go to the next slide, please.

8 I'd like to go to the ROMA slide on the log scale,

9 please, if we can. And what I want to show you is --

10 slide on -- okay.

11   What I want to show you is that if you look

12 at the cutoff line, which, in this case, is pre-

13 menopausal women, and it's at around 13 percent, what

14 you can see is that in Stage 1, 2 women, which is the

15 second column from the right, and compare it to Stage

16 3, 4 ovarian cancers, the ROMA value is significantly

17 elevated. It's not near the line in most cases. It's

18 significantly elevated. The values that are near the

19 line tend to be benign diseases and, in some cases,

20 borderline tumors or low-malignant-potential tumors.

21 So there is significant elevation of ROMA even in pre-

22 menopausal women, even in early stage disease, and

23 that's due to the contribution of HE4, not CA-125.

24   And if we can bring up the second slide on

25 post-menopausal women, you'll see the same thing there

1 as well. No, I know. I know I was asking for the

2 post-menopausal. Okay. Slide on, please. And you can

3 see the same thing in post-menopausal women as well.

4 Our cut point that we chose was 27 percent, and you can

5 see again in the right-hand column is Stage 3, 4, last

6 column to the right is Stage 1, 2, and you can clearly

7 see that values are significantly elevated for the most

8 part in these patients. And that's due to the

9 contribution of HE4.

10   There is another point I just want to make

11 briefly that we haven't talked about today that I think

12 is very important in terms of the ROMA test, and that's

13 that we're trying to change the use of biomarkers in a

14 significant way. We're not using a typical cutoff.

15 CA-125 uses a cutoff of 35, and I think all of us here

16 understand that there is nothing magical about that,

17 that, you know, below 35 doesn't mean not cancer and

18 above 35 means cancer. But it is often interpreted in

19 somewhat that fashion, and I think that's been

20 difficult to interpret.

21   What we're providing is a probability, and I

22 think one of the questions this morning was how would

23 this change the practice of medicine. And I think if

24 you present a patient with a probability of something

25 like 80 percent, I think that's very meaningful to the

1   physician and the patient whereas if you say your CA-

2   125 is 80, how do they really judge that? I think a

3   probability is something that people can really use,

4   patients can use, and physicians can use. I think it

5   changes the way that we use biomarkers in a fundamental

6   way and in an important way.

7   So having said all of that, I'd like to

8   introduce again Dr. Skates just to mention the

9   statistical analysis that was done by the FDA and to

10 compare and contrast that to our analysis.

11   DR. SKATES: Thanks, Dr. Allard. So there

12 are two reasons why the statistical analyses that was

13 presented by the FDA are not valid. The first is the

14 way that the trial was conducted was to start out with

15 a pilot study, two pilot studies. There, it was

16 deliberately chosen that a case control study enriched

17 for cases. So we had almost 250 cases in the pilot

18 study and a similar number of benign controls. That

19 gave us the power to see differences in sensitivity

20 between CA-125 and CA-125 plus additional markers.

21 Slide on the screen.

22   So you'll see that, in fact, 242 cases and

23 236 benign controls. And that group was a result of

24 the fact that we had half of the -- one of the pilot

25 studies was case control, over-sampled for cases. And

1 so, therefore, in a cohort study, there are many fewer

2 cases. There, in fact, was a total of 150 cases, and

3 slide on the screen.

4   And we can see the total number of cases here

5 is invasive epithelial cases are 129 and LMP tumors are

6 29. So that's 151. So the study is simply not powered

7 to look at differences between CA-125 and CA-125 plus

8 additional markers.

9   DR. BERRY: Can I ask a question,

10 Mr. Chairman?

11   DR. NETTO: Yes.

12   DR. BERRY: Dr. Skates, I've been confused

13 about which data are which. So Dr. -- the FDA doctor,

14 Kondratovich, most of what she was presenting, is it

15 correct, was on the pilot study?

16   DR. SKATES: No. All of it --

17   DR. BERRY: It was mostly on the --

18   DR. SKATES: All of it was on the pivotal

19 study.

20   DR. BERRY: All of it was on the pivotal

21 study? And what you were just showing, that was the

22 pivotal study?

23   DR. SKATES: That's correct. And the

24 previous slide was the pilot, combined pilot studies.

25   DR. BERRY: Okay. Thank you.

1   DR. SKATES: All right. So there's a lack of

2   power. The second issue, when you come to a lack of

3   power at the end of a clinical study and you go into

4   subgroup analysis, it is notorious for finding false

5   positive and false negative results by looking at

6   different subgroups. And that is a well-known fact.

7   So the power in the pivotal study was aimed

8   at ruling out sensitivities below 80 percent, across

9   all pre-menopausal, post-menopausal, early stage, late

10 stage LMP tumors. There was no power to look at

11 subgroup analysis. So those are the two reasons that

12 we find there's a difference between the FDA

13 presentation and what our results were. Power in the

14 pilot studies to look at differences between CA-125 and

15 additional markers and showing statistically

16 significant differences.

17   We did actually look at, in addition to the

18 ones that I presented, 80 percent power. And that was

19 done 2003 to 2005. So that's the time frame of the

20 study. When it came to actually doing the pivotal

21 study, clinical considerations were determined as to

22 what the appropriate specificity was. And that

23 appropriate specificity was 75 percent. It wasn't

24 actually one of the ones that we had chosen in our

25 pilot studies, but what the pilot studies will

1 determine was what adds to CA-125. What the pivotal

2 study is designed to do is rule out sensitivities below

3 80 percent across all the patients that are seen in

4 this referred population.

5   DR. NETTO: If I --

6   DR. BERRY: Was a cut point chosen on the

7 basis of the pivotal study?

8   DR. SKATES: So the specificity was chosen

9 a priori to the --

10   DR. BERRY: 75 percent?

11   DR. SKATES: 75 percent. But what that

12 corresponded to in terms of a cut point in the -- was

13 actually chosen from the pivotal study. In fact, as

14 the FDA pointed out, there needs to be a correction for

15 that particular choice of the way the cut point was

16 chosen. And they had -- there are two approaches that

17 we have recently looked at to examine the impact on the

18 confidence interval for the 75 percent specificity.

19 Slide on screen.

20   As the FDA had pointed out, the bootstrap is

21 one approach. We, in fact, also did use the Delta

22 method to look at the impact of this choice. So the

23 current 95 percent confidence interval ranges from 82.9

24 to 93.0 percent.

25   DR. BERRY: So this is to adjust for the fact

1 that you did not have a prospective trial evaluating a

2 pre-defined cut point?

3   DR. SKATES: A pre-defined cut point on the

4 probability, Predictive Probability, that's correct.

5 So slide on screen. Bootstrap samples, there were

6 10,000 draws with replacement from the linear

7 predictor. 75 percentile was calculated in the benign

8 patients and sensitivity in the cancer patients, and

9 the 95 percent confidence interval from that approach

10 ranged from 82.39 percent, so that is lower than the

11 current confidence interval for the sensitivity, and in

12 fact goes higher. So it is broader. It does take into

13 account the uncertainty in this.

14   The other approach that we used was the Delta

15 method. And slide on screen. There we looked at -- we

16 used the fact that the variation in the sensitivity can

17 be split into two terms, the average variation of

18 the -- of the sensitivity given a cut point plus the

19 variation in the average sensitivity given that cut

20 point. And the first term is approximately the

21 standard binomial variance of sensitivity times one

22 minus sensitivity divided by the number of cancer

23 patients. The second term you can approximate using

24 the Delta method, which is getting the variance of a

25 function of a random variable. And that essentially is

1 that combination of terms you see below.

2   There is the Delta method and then there is

3 the asymptotic variance of a percentile. And that then

4 gives us a variance, which when multiplied by 1.96

5 gives us a 95 percent confidence interval, and that

6 confidence interval goes from 82.4. So, again, lower

7 than what we had seen, but not much, and up to 95

8 percent. So it is a little bit broader. And the point

9 is that these two approaches, independent approaches to

10 allow for the fact that the cut point was on the

11 Predictive Probability scale for the 75 percent

12 specificity was chosen on the pivotal study.

13   But in comparing to the current 95 percent

14 confidence interval, you can see it is a little bit

15 broader but still clearly rules out any sensitivities

16 below 80 percent.

17   DR. BERRY: Mr. Chairman, can I follow this?

18   DR. NETTO: Sure.

19   DR. BERRY: So what you are saying,

20 Dr. Skates, is that some of what Dr. Kondratovich

21 indicated was not correct in the sense of the subset

22 analyses. I mean, exactly which analyses are you

23 objecting to? And, in particular, the issue of adding

24 HE4 to CA-125, which I think is critical, her analyses

25 suggested that maybe there was not a statistically

1 significant benefit. You had indicated earlier in

2 response to Dr. Netto that in the pilot study, it was

3 statistically significant adding H -- did you in the

4 pivotal study -- you said the pivotal studied was not

5 powered, but was there at least a suggestion that HE4

6 was adding something?

7   DR. SKATES: So let me take a couple of

8 issues. That is a couple questions. What I was trying

9 to address in the FDA's presentation was there was a

10 number of slides where there's a comment that the cut

11 point chosen in the pivotal study introduces extra

12 variation in our confidence interval for sensitivity.

13 I am showing with these two slides --

14   DR. BERRY: Yes, yes, and --

15   DR. SKATES: -- what that was.

16   DR. BERRY: Okay.

17   DR. SKATES: So that's still ruled out, our

18 primary objective of ruling out sensitivities below 80

19 percent. My objection -- and that's what it was

20 powered to do. You need to get high enough sensitivity

21 point estimate and narrow enough confidence intervals

22 to then rule out that 80 percent and below.

23   DR. BERRY: Yes, I understood that. But what

24 I was asking about --

25   DR. SKATES: And the power --

1   DR. BERRY: -- is what others of her analyses

2   are you objecting?

3   DR. SKATES: So what I'm objecting to is the

4   subgroup analysis of comparing ROMA to CA-125 in the

5   early stage versus -- in the early stage, in the late

6   stage, in the pre-menopausal, in the post-menopausal,

7   any subgroup or combination that she showed was

8   underpowered because the power was there for the

9   original goal and not for looking at subgroup analysis.

10 That's why we had a case control study deliberately

11 over-sampled in the pilot studies.

12   DR. BERRY: So I agree with some of that, and

13 I think she would agree as well, but there -- so with

14 respect to stage of disease, but with respect of pre-

15 menopausal versus post-menopausal, it really looks like

16 a different kind of a marker. And, indeed, you get a

17 very different model in the two diseases, one in

18 which -- in the two circumstances, one in which HE4 is

19 huge and dominates CA-125, and in the other one, in the

20 post-menopausal, where CA-125 seems to be carrying the

21 day. So to look at those things separately I don't

22 think is a bad thing.

23   DR. SKATES: Nonetheless -- so the reason we

24 chose sensitivity over the -- all the patients was that

25 what we wanted to address was in a typical practice

1 where we see referred patients, where we see post-

2 menopausal and pre-menopausal patients, we want to know

3 what was the expected number of cancer cases that ROMA

4 would get right, and was that at a high enough level.

5 And so, therefore, that was how the study was powered.

6   We expected to see at least 100 cases of

7 ovarian cancer, and we saw in the end 150 out of the

8 500. We know that the pre-menopausal number of cases

9 is much fewer. And we were not aiming to power the

10 study for separate subgroups of the population. Our

11 aim was to say in a typical population that a

12 gynecologic oncologist would see with pelvic masses,

13 what fraction of cancers would ROMA get right?

14   DR. BERRY: Right. Thank you.

15   DR. NETTO: Would the FDA like to comment on

16 the bootstrap and Delta especially?

17   DR. KONDRATOVICH: I would like first clarify

18 about selection of the cutoff in the validation study.

19 I think that we don't have very big problem with this

20 approach because we know that cutoff will be provide

21 unbiased destination. Variability will be only little

22 bit more. Why? Because, really, we have enough

23 sample, like, for example, for pre-menopausal, 200

24 subject which are benign, so 75th percentile is

25 relatively good estimated.

1   So I -- with bootstrap. It was not very big

2   increase in variability, but because we did not obtain

3   any statistical significance, it was really no big

4   issue to recalculate all this confidence interval. So

5   you saw I put on there, like, note that, yes, there are

6   some maybe half percent or little bit larger.

7   But, again, I would like emphasize that the

8   training set was used in order to obtain this weight,

9   in order to obtain this classifier. So really what we

10 need to have, performance in the validation dataset,

11 and we did not see. So we obtain absolutely the same

12 performance of the ROMA test like with CA-125. Why I

13 consider subgroup analysis Stage 1 and 2? It was

14 suggested in the Sponsor's submission. It was a lot of

15 analysis, and it was from Sponsor's point of view that

16 HE4 made some contribution for the Stage 1 and 2

17 epithelial ovarian cancer. This was the reason that I

18 included this analysis.

19   DR. NETTO: Thank you. Go ahead. You can

20 address --

21   DR. BECKER: So, briefly, this aspect of the

22 relative contribution of the two markers to the

23 performance of the assays actually have distinctly

24 lesser importance to us, I think, than is the question

25 of the overall performance of the test, in terms of as

1   the device is constructed being able to separate cancer

2   from noncancer patients. That said, we would have been

3   quite interested in being able to see a difference with

4   respect to the two markers showing up in the pivotal

5   study as it was carried out. Having not found that

6   difference, one could recognize, doesn't demonstrate

7   explicitly that there was not a difference that exists

8   if you had a high enough population of patients there.

9   It's not something which is actually testable and, as I

10   think has been described, that wasn't a hypothesis that

11   had been put forward by the Sponsor. However, we were

12   not reassured by the inability to find such a

13   difference.

14   In the assertions with respect to a

15   difference being present in the pilot study, the two

16   concerns that sort of stick out for us were that we're

17   not aware of their having been a pre-specified

18   hypothesis for looking at the explicit contribution of

19   one marker versus another in that study and that the

20   difference that was brought out was at a cut point, a

21   point in the trade off between sensitivity and

22   specificity that is quite distant from the cut point

23   that is being used for the test as it would be

24   deployed.

25   So that even if one sees -- even if one were

1 to follow on what looks like the suggestion, though not

2 statistically significant, in the curves for the

3 pivotal study that would suggest maybe at very high

4 specificity there is a hint of their being something

5 for some sub-analyses, that would suggest there is help

6 from HE4, okay, those were at a point which is quite

7 distinct from where this assay is expected to operate

8 in practice.

9   So we just could not come away with a

10 conclusion that, yes, both markers are helping out for

11 the assay as it will be deployed. That, however, is,

12 as I say, a secondary issue compared to the question of

13 whether as used, as constructed, the test does separate

14 cancer from noncancer patients.

15   DR. BERRY: Can I ask about that?

16   DR. NETTO: Let me -- this case first --

17   DR. BERRY: Dr. Becker, so I agree, but

18 suppose you do the entire set and it turns out that HE4

19 and CA-125 both add substantially? But then you look

20 at pre-menopausal and CA-125 doesn't add, and you look

21 at post-menopausal and HE4 doesn't add. So maybe you

22 should build a model -- and I'm taking a really extreme

23 position that I hope everybody will comment on -- that

24 you should use HE4 in pre-menopausal and CA-125 in

25 post-menopausal and not combine them?

1   DR. BECKER: Well, I don't know that -- I

2   wouldn't comment on that from a formal statistical

3   perspective in terms of that kind of divergence of the

4   way that you would treat the two patient populations

5   except to state that absent stepping away from the

6   question of HE4 and CA-125 adding to each other, it

7   does appear -- and, in fact, the models were

8   constructed to treat those two populations, pre-

9   menopausal and post-menopausal, differently. And I

10 think that is surely a relevant thing to consider in

11 terms of how the test might be used because, as

12 Dr. Kondratovich pointed out, when you look at the

13 pooled sensitivities and specificities, the pooled

14 performance, you're looking at unequal weighting with

15 respect to the prevalence of the pre-menopausal and the

16 post-menopausals in that overall population. So there

17 is likely some concern to be delved into there with

18 respect to how those sub-populations might fare

19 differentially as the test would be applied in

20 practice.

21   DR. NETTO: Thank you.

22   DR. BERRY: So the unequal weighting in

23 different models, if you look at the lines, in the

24 post-menopausal you see a roughly diagonal line --

25   DR. BECKER: Ah --

1   DR. BERRY: They're contributing similarly.

2   In the pre-menopausal, it's essentially HE4.

3   DR. BECKER: Yes, but realize there that that

4   line is the best model as fit for that dataset --

5   DR. BERRY: I understand.

6   DR. BECKER: But there was a host of models,

7   and, in fact, one dealing with CA-125 only, which is

8   insignificantly different. So the way that the -- you

9   give the algorithm the task of handing you back some

10 coefficients, it will hand you back the coefficients

11 which are the very best fit for that dataset. But that

12 doesn't mean that there won't be other coefficients,

13 for example, dealing with CA-125 alone that perform

14 darn nearly as well.

15   So that that's where the idea of being able

16 to determine specifically whether there is a difference

17 in the performance with respect to those different

18 combinations of variance actually fits in there. It's

19 clear that for this dataset, that that nearly

20 horizontal line must have been the best fit to the

21 data, but it's a reasonable question to ask whether

22 that line is a whole lot better than a number of other

23 lines that could have been drawn through that set.

24   DR. BERRY: Yeah, I'm sure Dr. Skates is

25 chomping at the bit to answer my question.

1   DR. SKATES: Yes. Thank you. So two

2   comments on that. There was a question about whether

3   there was an a priori in the training of two pilot

4   sets, whether there was an a priori hypothesis as to

5   whether HE4 added to CA-125. And, no, there wasn't.

6   We had 15 markers that we were looking at. And so we

7   ended up trying to choose the best.

8   There was an attempt -- there is always a

9   problem in the same dataset of coming up with an

10   algorithm or a combination of markers of over-fitting.

11   And the only method that I am aware of that tries to

12   address that is cross-validation. And we used to leave

13   one out cross-validation to see if we still had a

14   significant contribution of HE4 to CA-125. That was

15   our best attempt at coming up with -- instead of having

16   a completely separate 500 another separate samples to

17   determine whether HE4 added to CA-125 from that

18   training set.

19   Once you come up with an algorithm, you then

20   want to evaluate that. There are going to be other

21   algorithms that are going to be near that algorithm

22   that are going to provide, in any subsequent down-the-

23   line set, post hoc analysis, that are going to have

24   operating characteristics very similar to the algorithm

25   that you've chosen.

1   But that's not the purpose of a validation

2   set to then try and cherry-pick and find the best

3   algorithm that separates out the cancers from the

4   controls. It's to validate the algorithm you came up

5   with in your training set, and that's what we did.

6   DR. BERRY: But, Steve, that doesn't address

7   my question --

8   DR. SKATES: Right.

9   DR. BERRY: If you do an analysis on the

10 bases of all of the data, you could very well find that

11 HE4 plays a major role, CA-125 plays a major role, and

12 you can't do without either one of them. But if you

13 separate the population in two and HE4 is playing a

14 role only in one sub-population we can identify very

15 well, pre-menopausal, maybe that that's the only sub-

16 population that it's adding in, and so you don't need

17 the ROMA in that group. All you need is HE4. And,

18 similarly, for the other group. The question --

19   DR. SKATES: Okay.

20   DR. BERRY: So the question that

21 Dr. Kondratovich asked was what about the post-

22 menopausal? Is it appropriate to add or is it

23 necessary to add HE4 in the post-menopausal. There is

24 some suggestion of it, but, as she indicated, it's not

25 statistically significant.

1   DR. SKATES: Right. And so we're not --

2   there's a problem with power there.

3   DR. BERRY: I understand.

4   DR. SKATES: So the way we approached it was

5   that there was -- in the post-menopausal group, there

6   was equal -- approximately equal weighting between HE4

7   and CA-125 in the logistic regression. All of those

8   coefficients, both of those coefficients, were

9   statistically significant. Whether in a nonparametric

10   test in a subpopulation you can show a significant

11   difference or not, that's another matter for a bigger

12   study. But there certainly was a positive increase of

13   ROMA to CA-125, even if it wasn't statistically

14   significant.

15   DR. NETTO: Dr. Berry --

16   DR. SKATES: So HE4 clearly --

17   DR. BERRY: Yes?

18   DR. SKATES: -- adds to CA-125 in the post-

19   menopausal group. In the pre-menopausal group, we

20   didn't want to throw -- HE4 dominates. That's clear.

21   And it does better than what the current ACOG usage

22   recommends, which is CA-125 greater than 200. And it

23   does better because HE4 has got a lot better

24   properties. We didn't want to throw out CA-125 because

25   it is certainly recommended in the ACOG guidelines.

1 But we gave it the appropriate weighting. So by giving

2 HE4 and CA-125 a predictive index, Predictive

3 Probability for post-menopausal women and pre-

4 menopausal women to the physician and then thereby to

5 the patient, they can then incorporate into the

6 clinical judgment of the scenario in the most

7 appropriate way.

8   DR. NETTO: Thank you. I think we will have

9 to cut it because we deliberated enough. I would like

10 to see if any other Panel members have a question of

11 the FDA --

12   DR. BRACCO: I'd just like -- can I just make

13 one comment that we all need to just make sure that CA-

14 125 is not indicated for use in determining the type of

15 surgical intervention that should happen. So I'm not

16 sure of the merits of these discussions, but it's

17 important to keep that in mind, that differentiating

18 between pre- and post-menopausal --

19   DR. NETTO: Correct -- monitoring.

20   DR. BRACCO: -- women is not a reality.

21   DR. NETTO: Correct. Go ahead, Dr. Freedman.

22   DR. FREEDMAN: I think there's been a lot of

23 discussion about separating the groups by pre- and

24 post-menopausal status. And I notice that in some

25 point in your study, you decided to test a certain

1 portion of the patients, not all of them, but a certain

2 portion of the patients for the FSH levels. Now, I'm

3 sure you're aware, there is a lot of variability in FSH

4 levels, and even several years before periods

5 disappear, FSH levels can go up, indicating an

6 ovulatory state that's in recent literature. I'm not

7 an expert in endocrinology. It's just from my reading.

8   But I wondered whether the FDA considered

9 asking a endocrinology opinion on the selection of this

10 endpoint, particularly based on one sample determining

11 whether those patients would go into the post-

12 menopausal or the pre-menopausal group. And the other

13 thing is would it have been better to have tested all

14 the patients or why just the one subset of patients.

15 And this is I think going to be -- because it's also a

16 question -- what was your definition of menopausal when

17 you designed the pivotal study, and did it change when

18 you went into the final study?

19   DR. NETTO: And I would add to that what

20 would the reclassification, how much effect did it have

21 on the results?

22   DR. MOORE: So when we designed the pivotal

23 trial, we did have statements on what would be

24 considered as pre- and post-menopausal from clinical

25 standards. And when we did the study, we had a certain

1 number of patients that actually had a hysterectomy.

2 Slide up, please.

3   So in the trial, our definition was post-

4 menopausal was a last menstrual period of greater than

5 12 months prior to the blood draw. And this is an

6 accepted standard for definition of menopausal status.

7 Or if their last menstrual period was unknown, then the

8 patient who was greater than age 56, which is the upper

9 95th to 99 percentile, these patients were considered

10 post-menopausal. If they were less than age 49, then

11 they were considered to be pre-menopausal.

12   So the patients that we had to run the FSHs

13 on, they had had a hysterectomy at some point prior to

14 being enrolled on the study. And we could not

15 determine truly when their last menstrual period was

16 from, you know, from the study because they had had a

17 hysterectomy.

18   Now, we know that menopausal status is not

19 determined by when you have the last menstrual period.

20 That's just an indicator. The menopausal status is

21 determined by the function of the ovary. So,

22 initially, these patients had a last menstrual period

23 when they had a hysterectomy, and that was greater than

24 a year. Yet, some of these patients were less than 30.

25 So for those patients that had a hysterectomy, we did

1   go ahead and perform FSHs on these patients in order to

2   correctly classify them.

3   When we looked at and had these patients

4   reclassified, the changes from -- for the sensitivity

5   actually were not in our favor. It went down from

6   about 91 percent to about 89.7 percent. I'd like

7   Dr. Allard also to talk.

8   DR. ALLARD: Yeah. I only wanted to amplify

9   what Dr. Moore just said, that the trial did from the

10 outset, a priori, was designed to measure menopausal

11 status. We realized later on that there were patients

12 that we could not categorize their menopausal status

13 because of their hysterectomy. We felt that it was

14 very important, in fact, to include them in the study.

15 We did not want to exclude patients. And, therefore,

16 we did do FSH testing on only that subset that we

17 couldn't categorize according to these criteria, which

18 we think are well-accepted.

19   DR. FREEDMAN: -- follow-up.

20   DR. ALLARD: Go ahead.

21   DR. FREEDMAN: So would you advise the FSH be

22 done along with the -- in those patients around that

23 level in order to make a decision? And what kind of

24 FSH testing would you recommend? A single-level or

25 multiple levels as are generally done by the endocrine

1 community?

2   DR. ALLARD: I'll ask Dr. Moore to answer

3 that from a clinical perspective.

4   DR. MOORE: So from a clinical perspective,

5 using the patient's history and their physical along

6 with all their symptoms that they have, the majority of

7 patients you're able to accurately identify whether

8 they're pre-menopausal or post-menopausal. It's very

9 rare that we use FSH testing to determine menopausal

10 status. We used, and I'll let Dr. Skates address why

11 we used the FSH test that we did and what the cut

12 points were, but we used a cut point in the Architect

13 FSH that in the FDA panel, they had -- or in the

14 handout, they had used as a cut point for a normal FSH

15 for post-menopausal patients.

16   So I think the majority of patients, the

17 physician who is seeing that patient will be able to

18 determine whether they are post-menopausal or pre-

19 menopausal, and it would only be a small amount of

20 patients where you truly have to get an FSH. I'll let

21 Dr. Skates address --

22   DR. FREEDMAN: The other issue was whether it

23 would have a -- what kind of confounding effect could

24 it have if you were wrong? In other words, if the FSH

25 level that you saw was incorrect because it just

1 represented a single time point and did you consider if

2 there could be confounding effects on the outcome of

3 the study by using the FSH on a selected population? I

4 wonder if this issue was of concern to the FDA as well.

5   DR. MOORE: I'm not sure if I can exactly

6 address that question, but, you know, for -- when we

7 look at FSH being used to determine menopausal status,

8 if the -- if you use a cut point, for instance, of 22

9 or 30, all of those -- especially at 30, all of those

10 patients will be post-menopausal. And you're right.

11 So in post-menopausal patients, there is not a lot of

12 variability to their FSH. In pre-menopausal patients,

13 there can be.

14   DR. FREEDMAN: You could have an elevated FSH

15 level in someone who was ovulating who had had a

16 hysterectomy. So --

17   DR. MOORE: Right. And that's why using a

18 cutoff of 22 is more appropriate because you're going

19 to identify or be able to identify more accurately

20 patients that are pre-menopausal as well.

21   DR. NETTO: Thank you. FDA?

22   DR. BECKER: So as the review had proceeded,

23 we had just noted that there was this issue with

24 respect to an evolution of the menopausal status

25 determination criteria. Dr. Reeves could perhaps speak

1 to more detail. But I don't think it's really

2 necessary other than to simply confirm what I believe

3 Dr. Moore indicated, which was that, in having seen

4 patients for this dataset change their menopausal

5 status, about 39 of them flipped as a result of that,

6 that the performance characteristics of the test as

7 measured did not change materially, okay?

8 So the concern that was more raised in our

9 minds is that if there are other means by which

10 menopausal status might be determined by a wide variety

11 of practitioners in a wide variety of settings, might

12 there be a risk that there can be a drift in the

13 performance of the test? And if that -- and that's why

14 we posed the question to the Panel to try to understand

15 whether this is a significant concern.

16 DR. REEVES: Additionally, if they use the

17 wrong equation as a result.

18 DR. BECKER: Well, the issue would be, of

19 course, that in having determined a menopausal status

20 that went from pre to post that you apply a different

21 equation, as Dr. Reeves indicates. Though, in this

22 dataset, having applied the different equation did not

23 significantly --

24 DR. NETTO: Still did not --

25 DR. BECKER: -- alter the positive predictive

1 value and negative predictive value of sensitivity and

2 specificity of the test as measures for this dataset.

3   DR. NETTO: Okay.

4   DR. BECKER: But if there is heterogeneity in

5 the community about the means by which menopausal

6 status might be assessed and we have no bounds on that,

7 our question to Panel is really aimed at trying to

8 assess whether bounds need to be prescribed for the

9 technique by which menopausal status is established.

10   DR. NETTO: Okay. Thank you. Any other

11 comment? Good. Anybody else from the Panel has a

12 question?

13   DR. BERRY: Can I ask?

14   DR. NETTO: I guess so.

15   DR. BERRY: I will not --

16   DR. NETTO: One more.

17   DR. BERRY: I will not ask something we've

18 already talked about except I want to go back to --

19   DR. NETTO: To the same question --

20   DR. BERRY: Earlier, a lot earlier. The

21 population and the indication -- and so Dr. Becker, in

22 his presentation, said that the positive predictive

23 value and the negative predictive value depend on the

24 prevalence. But, of course, the sensitivity and

25 specificity may or may not depend on the prevalence.

1 So is the indication for adnexal masses or is the

2 indication for adnexal masses that are referred to a

3 tertiary center or something in between? Just my back

4 of the envelope calculation is that what you've looked

5 at is something like 10 percent of adnexal masses. So

6 those that have the high-risk associated with having a

7 greater prevalence of cancer.

8   DR. ALLARD: Yeah, let me just try my best to

9 answer that. First, the population clearly was

10 patients already referred. And that is the population

11 that is described in the intended use. So the intended

12 use describes a population of patients that are

13 referred. However, in terms of the population that we

14 actually measured, we really don't know what proportion

15 of patients are referred or not referred. There isn't

16 literature data to guide us on that, and we didn't

17 study it in our study.

18   However, there is one aspect that we did look

19 at very carefully, and that's what was -- what did our

20 population look like? Did it look like a population

21 that is described in the literature for a population of

22 women with pelvic mass or had we selected a very small

23 subset that might be on an extreme edge of that

24 population?

25   And the answer is, it's not at an extreme

1 edge. It's quite representative. The published

2 proportion of women with epithelial -- invasive

3 epithelial ovarian cancer in women with pelvic mass is

4 13 to 21 percent. Our study was 24 percent. So we did

5 enrich for cancers, and we did that deliberately. That

6 was part of our endpoint was to enrich for cancers. So

7 we did have a slightly higher proportion of cancer, but

8 not greatly higher.

9   And, also, as Dr. Moore pointed out this

10 morning, the spectrum of benign disease that was seen

11 in our study is very representative of the spectrum of

12 benign disease you would expect to see in women with

13 pelvic mass. And as he pointed out much more

14 eloquently than I can, the types of diseases are very

15 representative. And they were not -- in fact, you can

16 put that slide up, please.

17   This is the spectrum of benign disease, and

18 Dr. Moore commented on it, and I can't comment on the

19 particular disease, but what we do know is that these

20 really cover the spectrum of benign disease that one

21 would expect to find. So it didn't look like our

22 population was skewed, certainly not from a

23 histopathological perspective.

24   DR. BERRY: That doesn't jive with the

25 numbers that I understood. Dr. Moore indicated that 20

1 percent of women at some time in their lives have a

2 pelvic mass.

3   DR. ALLARD: Correct.

4   DR. BERRY: And so if you break that out into

5 an annual rate and you incorporate the fact that you

6 had 25 cancers in your pivotal study, that would equate

7 to something like 1 in 20 patients, 1 in 20 women

8 eventually having ovarian cancer. And as we heard from

9 the earlier presentation, it's 1 in 58. So something

10 is off by a factor of three. It seems to me that

11 the -- something is not fitting there.

12   DR. LEVY: And can I take that just one step

13 further? When you talk about how this compares to the

14 published literature, are we talking about population-

15 based data or publications that likely are coming out

16 of tertiary care centers, which would obviously be

17 skewed for population-based data. And related to that,

18 do you have any idea, in terms of I believe your two

19 centers doing this, how your population compares to

20 other referral centers?

21   DR. SKATES: I want to --

22   DR. NETTO: Go ahead, Dr. Skates.

23   DR. SKATES: I'd just like to address the

24 factor of three. Five to ten percent of women in their

25 lifetime will have a pelvic mass, not 20 percent.

1   DR. BERRY: Oh, okay.

2   DR. SKATES: Okay? So that should deal with

3   the --

4   DR. BERRY: So his presentation was wrong?

5   DR. SKATES: Twenty percent --

6   DR. BERRY: All right. Five percent would

7   fit.

8   DR. SKATES: Twenty percent of women with a

9   pelvic mass have ovarian cancer. I'm thinking that

10   that's where the 20 percent came from. So somewhere is

11   a miscommunication, but --

12   DR. NETTO: Dr. Levy?

13   DR. LEVY: Yeah, I really want to address a

14   fundamental question that we really haven't talked at

15   all about today, and that is the definition of a pelvic

16   mass. And this should be self-evident, but it isn't

17   because at least in my clinical practice, I would say

18   25 to 35 percent of the women that I see referred for a

19   so-called pelvic mass have an incidental finding on CT

20   scan, MRI, some other thing, and I'm noticing that 20

21   percent of your patients had a simple cyst, paraovarian

22   cyst or a functional ovarian so-called mass that was

23   either a functional cyst or a corpus luteum.

24   And I'm really disturbed by a lack of

25   definition. What are we calling a pelvic mass? What

1 was the distribution of the size of these tumors that

2 we're talking about? I mean, to be clinically

3 effective, we need a test that's going to distinguish

4 those that seem to be benign but in fact require

5 surgical intervention.

6   DR. MOORE: I agree with you. It's very

7 difficult to define a pelvic mass. And in our

8 community of gynecologists, some people will call an

9 ovarian cyst that's two centimeters a pelvic mass.

10   DR. LEVY: Well, the radiologists do.

11   DR. MOORE: And I didn't want to pick on the

12 radiologists.

13   (Laughter.)

14   DR. MOORE: And so you're right. It is very

15 difficult. And also to address a point on this side,

16 many of these will resolve on their own. And so even

17 though many women will present with an ovarian cyst or

18 a pelvic mass, if you give them a few months, those

19 cysts will regress.

20   Now, we defined a pelvic mass. We actually

21 defined it as pelvic mass or ovarian cysts in our

22 trial, so we didn't put a size characteristic on it.

23 We didn't put a complexity onto this. But what we did

24 indicate was that all of these patients were going to

25 surgery. Now, they weren't going to surgery because of

1 the trial. They were going to have surgery because of

2 their symptoms and the presence of an ovarian cyst or

3 pelvic mass. And when it was determined that they were

4 going to have surgery, that's when they became eligible

5 for the trial.

6   So, you know, there were a lot of patients

7 that probably weren't referred into the trial because

8 they resolved, and we also saw that a few patients that

9 were on the trial, when they came up to time for

10 surgery, their cyst had resolved. And so I think you

11 make a very good point that in our benign population,

12 the spectrum of disease is probably very similar to

13 what you would see in your practice. You would see

14 endometriosis and dermoid cysts and paraovarian cysts,

15 and some would be symptomatic and others would not.

16 But that's the definitions that we use for the trial.

17   DR. NETTO: Thank you. So at this point, any

18 further discussion from the Panel, deliberation of --

19   DR. JASON: Let me just ask my question again

20 because it seems to me if you are saying this should be

21 used by the sub-specialists, do you have data to

22 support that your populations of patients are

23 comparable to what other centers are seeing?

24   DR. ALLARD: I think the best answer to that

25 is that we utilized 14 different centers, and they were

1 geographically spread throughout the United States.

2   DR. JASON: And there are how many centers

3 total.

4   DR. ALLARD: Fourteen.

5   DR. JASON: Oh, so this -- in the United

6 States, this is --

7   DR. ALLARD: This was a multicenter --

8   DR. JASON: -- all the centers?

9   DR. ALLARD: Multi-center, prospective

10 style --

11   DR. JASON: So this is all the centers in the

12 United States?

13   DR. ALLARD: Oh, I don't know how many -- I'm

14 not certain at all how many centers there are total in

15 the United States, but we utilized 14.

16   DR. JASON: Um-hum.

17   DR. ALLARD: And they were geographically

18 dispersed throughout the U.S. and gave us a reasonable

19 mix of ethnicities as well.

20   DR. JASON: Okay.

21   DR. NETTO: Dr. Freedman?

22   DR. FREEDMAN: It occurred to me, in

23 selecting patients for the study, do you have the

24 histories on these patients to see what types of

25 clinical evaluation they had, including CA-125 levels

1 that were done by the referring doctor or by the

2 center, and do you have that data?

3 DR. ALLARD: We did not collect data on their

4 original CA-125 levels. We collected data only at the

5 referral center. We did not collect data at the

6 referring center, if you will.

7 DR. FREEDMAN: Because, typically, if they

8 were following the SGO guidelines, they would be using

9 the CA-125 as part of a clinical evaluation of these

10 patients.

11 DR. ALLARD: Our expectation is that

12 virtually all of these patients would have had a CA-125

13 measurement and that that would have been part of what

14 was used to refer them on.

15 DR. FREEDMAN: It would be interesting to

16 know how they performed.

17 DR. NETTO: Dr. Levy?

18 DR. LEVY: I guess I'm still having a problem

19 with the intended population, which are patients who

20 are already referred to a GYN oncologist and already

21 scheduled for surgery either because they're

22 symptomatic or because there is some elevation. I

23 don't see the utility in the test. I mean, the

24 patients are already in a referral center, and they're

25 already scheduled for surgery. So I guess I'm slow and

1 I'm just a general gynecologist, but I don't see a

2 utility.

3   DR. MOORE: You're not slow because you're

4 just a general gynecologist. Actually, you're probably

5 a lot smarter than the GYN oncologists. Everything

6 that you stated in terms of the population is correct.

7 But as gynecological oncologists, this test is going to

8 be valuable for us because it allows us to do a number

9 of things and gives us information to do that.

10   For instance, operating on a patient with a

11 low-risk cyst would be a laparoscopy. And having that

12 cyst in a bag and rupturing it inside the abdomen in a

13 low-risk situation would be much more acceptable than

14 if that were to happen in a high-risk situation, where

15 we would be advancing the stage of their disease. It

16 helps us to pick out surgical approaches. Laparoscopy.

17 Nowadays, there's a lot of people using robotic

18 surgeries and laparotomy.

19   In the terms of pre-operative planning, you

20 know, for very, very ill patients that have pelvic

21 masses, like an 83-year-old that has many comorbid

22 medical conditions, I would like to know whether I'm

23 going to have to be managing this patient in an ICU

24 setting afterwards because I've done a big laparoscopy

25 [sic] or whether I can get away with a laparoscopy over

1 a laparotomy.

2   There're benefits to the patients. And to be

3 able to sit down and tell a patient and get an informed

4 consent with them on how they're going to do and what

5 we're going to do to them is very important. As a

6 patient goes to sleep, if they think they're going to

7 have a laparoscopy and go home that night, that's a

8 whole different counseling than for a patient that is

9 going to be getting a laparotomy and surgical staging

10 and is now going to spend five to ten days in the

11 hospital recovering and another six weeks before

12 they're at home. So there are a lot of benefits to

13 this.

14   And then as I pointed out in my

15 presentations, for those patients that have a very low-

16 risk, some of those patients would prefer to have their

17 surgery with the gynecologist that has been taking care

18 of them for years. Now, in our institution, we have

19 120 gynecologists. So it's very easy for me to say

20 with a low-risk patient, great, go ahead and have your

21 surgery. There is GYN/ONCs at this center. And if

22 there's a rare chance that you have an ovarian cancer,

23 they will call us into the OR. I will be available,

24 and we can do your cancer surgery at that point.

25   So all of these are issues where I think this

1 is vitally important for our patients, and it helps us

2 to manage them and give them informed consent.

3   DR. NETTO: So would you think that exact

4 scenario, that exact recommendation, should be included

5 in the labeling because if we're talking about a

6 test -- especially in a pre-menopausal. I know you

7 keep beating around the issue that the study was not

8 powered, the pivotal study was not powered, but at

9 least from the analysis of the -- there is a suggestion

10 that the test is not as good in the pre-menopausal

11 population. Now, and looking at the sensitivities that

12 we talked about this morning, 37 percent of LMPs in

13 pre-menopausal and 23 of all cancers in pre-menopausal

14 are going to be missed. That's a significant false

15 negative, in my opinion, at least, and we'll see what

16 the other Panel members think.

17   Now, having known that, I guess, like

18 Dr. Levy said, you're coming to a surgical oncology

19 center to be treated. And I think in the morning,

20 there were some suggestion that based on the ROMA, why

21 not go back to reverse referral issue that we talked

22 about. And I think that may offer the patient a way --

23 you don't know that these patients are not going to

24 fall through the crack. You don't know that now you

25 gave them a false reassurance when 23 percent of them

1 may really have cancer, even though 40 percent of those

2 are LMPs.

3   But I saw no details about the LMPs. Are

4 they invasive LMPs? Are they serous or mucinous, and

5 we'll come to this question in a second. So these

6 could be significant disease, not just LMPs, and

7 especially in a pre-menopausal woman.

8   DR. LEVY: And I think the extrapolation to

9 your center is not a good on.

10   DR. NETTO: Correct.

11   DR. LEVY: In that, you know, if you look at

12 Barb Goff's study in South Carolina, if you look at

13 where I live, which is a cosmopolitan center, but we

14 don't have a GYN oncologist at our hospital. So I may

15 be capable of doing the GYN oncology surgery. But the

16 patients we really need to capture in order to improve

17 clinical outcomes, which is what we're all about, is to

18 make sure that those patients who look like they're

19 low-risk get the right operation. And in many, many

20 places around the country where this will be used, the

21 nine ONCs who could just walk into the operating room

22 don't exist. You know, this is about referring a

23 patient 25, 50 miles away and about an intraoperative

24 decision-making process that doesn't include being able

25 to bring in a GYN oncologist at the last minute.

1   DR. MOORE: And I agree with that point to

2   some extent. But when you look at how many women would

3   potentially be affected by that, it is -- it's low.

4   It's 330 out of 11,000, when we look at our rate for

5   diagnosis of epithelial ovarian cancer.

6   You know, this test, you know, right now

7   we're talking about -- I was asked to talk about how it

8   would be used by gynecological oncologists. This is

9   how I would use it at my center. And I'm sure that

10 other gynecological oncologists would find benefit for

11 how they would use it, either if they were in private

12 practice as a gynecological oncologist -- I can't

13 speculate on that.

14   DR. NETTO: And that's exactly the point. So

15 as far as the wording of the labeling, I think that's

16 where the gist of it is because even mention that on

17 the phone when they call you trying to refer you, let's

18 throw in a ROMA test, and then the ROMA test is

19 negative, he may -- he or she may not send you that

20 patient anymore. And you didn't even see that patient.

21 So, basically, we use the standalone test that we have

22 no data on any clinical correlations and probably

23 encouraging that patient -- or discouraging from coming

24 to be seen by a specialist who she may be the one who

25 need to be seen. We don't know who is going to be in

1 this 37.5 percent, right, in a pre-menopausal,

2 especially in a pre-menopausal population.

3   I agree it seems, the data seems very good

4 for the post-menopausal with Stage 4 disease, but I

5 seriously doubt even if the test was negative in such a

6 patient that it's going to make a difference. I'm

7 bothered by the lack of the clinical correlation and

8 leaving this open scenario where, of course, you have

9 to integrate it with the rest of the clinical data.

10 Well, we all know as physicians that that has to be

11 done on any clinical test. So I don't feel that's

12 enough reassurance in the labeling for that. So that's

13 why I'm hammering on this issue.

14   How restrictive should we be in term of that

15 labeling because if the study was designed on people

16 that just were referred to oncology center, and they

17 were going to go and -- these people proceeded with

18 surgeries in oncology center. So then you have to

19 offer the test for the people -- the rest of -- in the

20 future for exactly the same population. And I'm not

21 sure that that's going to happen --

22   DR. LEVY: And the reality is, given how

23 frightened women are of ovarian cancer, it's very

24 likely to be used off-label. I mean, we have to -- the

25 reality is that even though we carefully craft the

1 labeling to say it is in patients who already have had

2 a decision for surgery and are in the hands of a GYN

3 oncologist, the reality is that once marketed, it's

4 unlikely to be used in that scenario. And my concern

5 is among that group of patients. I don't know how the

6 test will perform in that group of patients, and that's

7 my real safety concern is I don't know when the

8 prevalence is much lower how this will work.

9   DR. MOORE: Again, I can't speculate on that,

10 and I could only show you models that we showed

11 earlier, but I can't go there.

12   DR. NETTO: All right. Thank you. Yes?

13   DR. FUNKHOUSER: Is the test you -- this is

14 for Dr. Moore --

15   DR. NETTO: I guess it's you again.

16   DR. FUNKHOUSER: Dr. Moore? Yeah.

17   DR. MOORE: Sorry.

18   DR. FUNKHOUSER: I'll give you a chance to

19 sit down here in just a second. My understanding is

20 that this test is designed to triage GYN oncology

21 patients back to local gynecologists and the local

22 communities, is that correct?

23   DR. MOORE: That's what's in our labeling

24 because of the study population, correct.

25   DR. FUNKHOUSER: That was the trial design.

1 Is that the intended use of the test?

2   DR. MOORE: That is the intended use.

3   DR. FUNKHOUSER: Okay. Are you anticipating

4 expanding use of this test to include screening at the

5 community GYN level for the reverse flow, that is,

6 triage of GYN clinic patients in local communities to

7 GYN oncology specialty practices?

8   DR. MOORE: We're certainly considering a

9 study, and it's up to Fujirebio.

10   DR. FUNKHOUSER: Is that included in this FDA

11 approval?

12   DR. MOORE: I don't think that's what we're

13 talking about here today.

14   DR. FUNKHOUSER: Okay. All right. Well, I

15 think we can all agree with you that accurate staging

16 and maximal debulking of bona fide LMP and invasive

17 ovarian carcinoma patients is the goal. And so I just

18 have a question or two for you about that.

19   Your meta-analysis argued that maximal

20 debulking increases survival from 23 to 34 months. Do

21 you have any data to show that interval laparotomy,

22 that is, local operation discovery of a carcinoma,

23 referral to a GYN oncologist, second laparotomy with

24 accurate staging and maximal debulking, do you have any

25 evidence that that interval laparotomy approach reduces

1 the benefit from 34 months to some number that's lower

2 than that?

3   DR. MOORE: Well, yes, we do. There is a

4 number of data that show that if you have an aggressive

5 surgical debulking attempt and even if that's at a

6 second surgery before chemotherapy and you're able to

7 optimally cytoreduce, there is a positive effect.

8 Unfortunately, that patient would have had to undergo a

9 second surgery and all the risks that come with a

10 second surgery, including infections and DVTs.

11   There is also data out of Yale that shows for

12 some patients, they're diagnosed with, you know,

13 disease that doesn't get debulked, and they have what

14 we call an interval debulking. They get chemotherapy

15 for a couple of cycles and then undergo aggressive

16 cytoreductive surgery and then continue on with their

17 chemotherapy and complete that. And those patients do

18 equally as well. However, the Yale group has noted

19 that you have to have an aggressive surgical debulking

20 at the time of that interval debulking or there is no

21 benefit. Unfortunately, when we see those patients,

22 they end up having two surgeries and they're exposed to

23 the risks of having a second surgery.

24   DR. FUNKHOUSER: And I apologize to you --

25   DR. NETTO: But his question is there a data

1 to show that there is a difference between the ones who

2 complete debulking what's done of initial because they

3 were done by surgical oncologist versus the ones who

4 the complete debulking was done at the interval? We

5 agree there is -- any time you're having a second

6 surgery that's increase --

7 　　　　　　DR. MOORE: Yeah.

8 　　　　　　DR. NETTO: Is there a formal data showing

9 decrease in term of survival from 37 months that would

10 have been achieved under the optimal scenario? That

11 would help us determine some of the questions that the

12 FDA --

13 　　　　　　DR. MOORE: So, yes, there is. And, you

14 know, the chance or the percent number of patients

15 actually achieving an optimal cytoreductive surgery is

16 much higher with a GYN oncologist than it will be with

17 a general surgeon or a gynecologist.

18 　　　　　　DR. NETTO: But that's not the question

19 　　　　　　DR. MOORE: I'm trying to get there --

20 　　　　　　DR. LEVY: There is one paper, there is one

21 paper looking at doing the second operation and the

22 timing is critical. So the paper was about people who

23 had initial laparoscopy, were discovered to have a

24 cancer. If the second operation is done within a time

25 frame, and I think it was about three weeks, their

1 outcomes were the same. If they went six or seven or

2 eight weeks before their primary debulking procedure,

3 then their outcomes were not as good. So there is one

4 paper looking at that --

5   DR. MOORE: Yeah, and then there is also

6 many -- there is papers that show rupture of the cyst

7 at the time of the initial surgery advances the stage.

8 And those patients will end up needing chemotherapy.

9 And, you know, as GYN oncologists, we're very aware of

10 that and take these tumors out intact. And that's why

11 it's very important preoperatively to know what we're

12 dealing with.

13   DR. NETTO: And that's why it's very

14 important to not miss those 37 percent who may be sent

15 back also --

16   DR. MOORE: I don't know where the 37 percent

17 comes from.

18   DR. NETTO: It is exactly from the

19 calculation. It's 6 out of 16.

20   DR. MOORE: Is that 37 percent of the LMPs

21 you're referring to?

22   DR. NETTO: No, it's 6 -- yeah, 6 out of 16

23 LMPs --

24   DR. MOORE: Oh, so for LMP tumors?

25   DR. NETTO: Correct.

1   DR. MOORE: Well, I think, you know, when we

2   talk about LMP tumors, that's a whole separate category

3   than invasive epithelial ovarian cancers. LMP tumors,

4   regardless of the stage, whether it's a Stage 1 or a

5   Stage 3, those patients do not need chemotherapy. So

6   when I have an LMP -- a patient with an LMP tumor --

7   DR. NETTO: So it's okay to miss them? Is

8   okay to be done by a regular GYN person?

9   DR. MOORE: I think in some cases it is. And

10   many times, most of those patients are going to be

11   Stage 1, over 80 percent of them. And when they're

12   operated on and the tumor is taken out, and there is no

13   residual disease -- even if they were not staged and

14   they get referred in, they do not undergo a second

15   surgery for staging and they do not undergo

16   chemotherapy if they have a low-malignant-potential or

17   borderline tumor. So those patients don't get exposed

18   to chemotherapy with an unknown indication, and they

19   also don't undergo a second surgery.

20   DR. NETTO: How about the 1 out of 7 Stage 1

21   to 2 invasive tumor? Is that a negligible number, in

22   your opinion?

23   DR. MOORE: Yeah, you know, I think an

24   invasive epithelial ovarian --

25   DR. NETTO: In a pre-menopausal woman. This

1   is all in pre-menopausal.

2   DR. MOORE: I'm sorry. I missed the --

3   DR. NETTO: One out of seven in pre-

4   menopausal Stage 1 to 2 invasive, is that an

5   insignificant number that may be shunted back to the

6   GYN and not -- this is all from the pivotal --

7   DR. MOORE: Yeah. No, and I understand. You

8   know, 6 out of 7 were accurately identified.

9   DR. LEVY: I think there are a couple of

10   issues with respect to the low-malignant-potential

11   tumors. That's very nice in retrospect. Once again,

12   as a general gynecologist operating in the operating

13   room with a pathologist, that is very dependent on the

14   accuracy of your pathologist, and it's a difficult

15   diagnosis to make on frozen section, particularly the

16   serous tumors. So I think that's problematic in that,

17   in retrospect, you can say it was a low-malignant-

18   potential tumor and it didn't make any difference. But

19   prospectively with respect to how you treat the

20   patient, I know from my standpoint, if I get told that

21   it's a low-malignant-potential serous tumor, I better

22   stage that as a cancer because there is a fair

23   percentage chance that when they do permanents, and you

24   could speak to that better than I can, that they're

25   going to change that diagnosis for me.