UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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IMMUNOLOGY DEVICES PANEL

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December 3, 2008
8:30 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

GEORGE J. NETTO, M.D.	Chairperson
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JANINE M. JASON, M.D.	Voting Member
TERRY R. LICHTOR, M.D., Ph.D.	Voting Member
DONALD BERRY, Ph.D.	Consultant
RALPH FREEDMAN, M.D., Ph.D.	Consultant
THOMAS JULIAN, M.D.	Consultant
BARBARA LEVY, M.D.	Consultant
ROBERT OZOLS, M.D., Ph.D.	Consultant
JOAN R. LONDON, M.A.	Consumer Representative
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MARTHA B. HOLLAND	Patient Representative
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I N D E X

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M E E T I N G

(8:30 a.m.)

DR. NETTO: I would like to call this meeting of the Immunology Device Panel to order. I'm Dr. George Netto, the chairperson of this Panel. I'm an Associate Professor of Pathology, Oncology and Urology at Johns Hopkins.

At this meeting, the Panel will be making a recommendation to the Food and Drug Administration on the 510(k) application K080033 for the Fujirebio Diagnostic, Inc. The HE4-EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum. The HE4-EIA used in conjunction with the Architect CA-125II assay creates a Predictive Probability of epithelial ovarian cancer using a mathematical function referred to as the Risk of Ovarian Malignancy Algorithm, or ROMA, for use in pre-menopausal and post-menopausal women with an adnexal mass who have already been referred to an oncologic specialist and are scheduled for surgery.

Subjects categorized as low risk for epithelial ovarian cancer using the ROMA value may have surgical intervention performed by a non-oncology specialist. The results must be interpreted in conjunction with other clinical findings in accordance

with standard clinical management guideline. The assay is not indicated as an aid in a decision to proceed to surgery.

If you haven't already done so, please sign the attendance sheets that are at the registration table. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table. If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do so with Ms. Williams.

I note for the record that the members present constitute a quorum as required by 21 C.F.R., Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulation.

I would now like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. And maybe we can start on the right side.

DR. BRACCO: My name is Dan Bracco. I'm with Oxford Immunotech, and I'm the industry rep.

MS. LONDON: Good morning. My name is Joan

London, and I'm the consumer rep.

MS. HOLLAND: My name is Martha Holland. I'm a patient rep.

DR. BERRY: I'm Donald Berry, biostatistician, M.D. Anderson Cancer Center, chairman of the Department of Biostatistics and head of the Division of Quantitative Sciences.

DR. JASON: Janine Jason. I'm a physician, epidemiologist, immunologist, and I'm CEO of Jason and Jarvis Associates.

DR. OZOLS: I'm Bob Ozols. I'm senior vice president of Fox Chase Cancer Center. I'm a medical oncologist involved in ovarian cancer for clinical management.

DR. FREEDMAN: Ralph Freedman, professor of gynecologic oncology at M.D. Anderson.

DR. LI: My name is Dai Li. I'm a medical officer with the IVD. I'm also the Executive Secretary of the Immunology Devices Panel.

DR. JULIAN: I'm Tom Julian. I'm a gynecologist at the University of Wisconsin in Madison.

DR. FUNKHOUSER: Bill Funkhouser, director of anatomic and surgical pathology at University of North Carolina in Chapel Hill.

DR. LICHTOR: I'm Terry Lichtor. I'm a

neurosurgeon at Rush University in Chicago, and I do neurooncology and neuroimmunology research.

DR. LEVY: I'm Barbara Levy. I'm a private practice gynecologist in Seattle, Washington.

DR. CHAN: I'm Maria Chan. I'm the acting Division director for the Immunology/Hematology Devices in OIVD.

DR. NETTO: Now, Dr. Li, the Executive Secretary of this Panel, will make some introductory remarks.

DR. LI: Good morning. First, I would like to make a few general announcement related to today's activities. First, transcripts of today's meeting will be available from Free State Court Reporting, Incorporation. The telephone number is 410-974-0947. Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

And let me take the time to introduce our FDA press contact, Ms. Mary Long. Will you please stand in the back of the room there?

I would like to remind everyone that members of the public and the press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and wish to speak to FDA officials, please wait until after the Panel meeting

has ended.

Finally, as a courtesy to those around you, please silence your electronic devices if you have not already done so.

I will now read into the record the Conflict of Interest statement. The Food and Drug Administration is convening today's meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with federal ethics and conflict of interest law is covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public. FDA has determined that the members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has

authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of the 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the Panel will discuss the -- recommendation on a pre-market notification application for the Fujirebio HE4 ELISA kits and associated risks of a malignancy algorithm test. The

device is for use in pre-menopausal and post-menopausal women presenting with adnexal mass who have already been referred to an oncology specialist and are scheduled for surgery. The result must be interpreted in conjunction with other clinical findings in accordance with standard clinical management guidelines. The assay is not indicated as an aid in a decision to proceed to surgery.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dan Bracco is servicing as the industry representative acting on behalf of all related industry and is employed by Oxford Immunotech.

We would like to remind members and consultants that if the discussions involve any other products and firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants

to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

I will now turn the meeting back over to our chairperson, Dr. George Netto.

DR. NETTO: All right. Now, we'll proceed to the Open Public Hearing portion of the meeting. Prior to this meeting, six persons requested to speak in the Open Public Hearing portion. Three will speak in the morning, and the remaining three will speak in the afternoon. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate record what you're saying. Please state your name and the nature of your financial interests you may have in this or another medical device company.

Dr. Li will now read the Open Public Hearing Statement.

DR. LI: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral

statement, to advise the Committee of any financial relationship that you may have with the Sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the Sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. NETTO: All right. Now, Ms. April Donahue requested to speak as an ovarian cancer survivor. Ms. Donahue, are you present? Please be reminded that each presentation has ten minutes.

MS. DONAHUE: Good morning. I'm April Donahue, and I'm an ovarian cancer survivor. Oops. I hit the button already. There we go. And Fujirebio did ask if I would speak today, and they are paying for my travel.

I wanted to share with you today the importance of early detection in ovarian cancer because I was one of the fortunate people to be diagnosed in Stage 1 ovarian cancer when I was age 24. And a lot of

people think, well, that's awfully young, and it is, but there are other young ovarian cancer survivors as well. And so I feel compelled that I wanted to talk about all the ovarian cancer survivors that I've been privileged to meet over the years and how an early detection test will help them.

As I said, when I was 24, I was diagnosed, and I did have symptoms, and they were dismissed by four different doctors. I went from ultrasound to a different doctor, and they told me different things. But the symptoms did persist, and thank God that I did listen to my body and said, hey, something is just not right here. I really want to be sure what's going on.

Finally, the doctor said, okay, you're going to have surgery and have this cyst taken out, and nobody had mentioned ovarian cancer to me at all. So after I woke up, I thought, okay, I'm good to go. Unfortunately, about a month later, the doctor called and said, okay, we need to discuss your pathology report, and at age 24, I didn't really know anything about that, and it was ovarian cancer. It was in the early stages, but I did have another surgery, and thank God, it was all confined to that one ovary. I was able to have my daughter, who is now 14, and so, of course, I did have another ovary.

And then ten years after that, I started to have symptoms again. At that point, I had never seen or really didn't know too much about a gynecologic oncologist, who knew I had ovarian cancer, did not say anything to me about being concerned about ovarian cancer again. They said, "You need to see a GI doctor." And thank God that my family doctor really said to me, "No, I think you need to see a gynecologic oncologist," and I really am blessed that got to see a good one.

And he said, "Well, I think we can wait six months." And something was nagging at me again. And I said, "No, I think I'm done having kids. It's time to have, you know, the ovary taken out and not worry about it. And, sure enough, I woke up, and it was ovarian cancer again. So I just wanted to share that story with you because that is the frustrating struggle that many women experience when they do have ovarian cancer in trying to get diagnosed. I'm really sorry. These slides are very, very dark. I tried to make them teal.

So the overall five-year survival rate is only 53 percent. However, if people are diagnosed early, it's as high as 90 percent, and so that's really our goal is to get people diagnosed in earlier stages. However, less than 20 percent of people are diagnosed

early. And, you know, the survival rate is just appalling for people diagnosed at late stages. And ovarian cancer, as you may know, is a leading cause of death among gynecologic cancers and 1 in 58 females born in 2007 will develop the disease.

And, you know, Barbara Goff did a wonderful study at the University of Washington, where she -- they study symptoms. And so women do have symptoms. And so knowing this, I think it really empowers us to be able to talk to women, and when I do talk to women about ovarian cancer symptoms, they'll say to me, okay, well, what can I do? And it's a frustrating part for me to say, "I'm sorry, you know, go see your doctor. Go see your gynecologist." But there's not really a test that they can go for to be screened, like we have the mammogram. There's really no test. So that's why I think that the test that you're discussing today is very important because a lot of these symptoms are misunderstood and are very vague. Everyone can have these symptoms from time to time, but it's if they persist that it can be a problem.

And a lot of women are under the misperception that they go to their doctor and they get their pap smear and that can detect ovarian cancer. And, of course, we know that's not true. And a lot of

women just don't have access and even know about a gynecologic oncologist. So that's why I'm excited about the test that you're going to be talking about today.

I also feel that the treatments for women with ovarian cancer are not quite what we want them to be, and I know the researchers are working very hard in that area, but the quality of life for women battling ovarian cancer is not wonderful.

And I wanted to show this final slide and just show you that if a woman goes to a gynecologic oncologist, she has a 97 percent chance of having complete surgical staging, and it can go down as low as 35 percent if she has it by -- her surgery done by a surgeon. So that's another reason why I feel, as a patient, that this test would be great for women because then they actually have something to go to their doctor and ask for and then be referred to a specialist who can help save their life. So I appreciate the Panel's time very much. Thank you.

DR. NETTO: Thank you very much, Ms. Donahue, for sharing your perspective. The next speaker is Dr. Carolyn Runowicz from the University of Connecticut Health Center.

DR. RUNOWICZ: Good morning, Mr. Chairman,

members of the Panel. I am honored to be able to speak with you today. I do want to tell you that my travel costs have been covered by the Sponsor as well as receiving an honorarium.

For my day job, I am a cancer center director at the University of Connecticut, and I am a practicing gynecologic oncologist. As a practicing gynecologic oncologist, I believe that it is imperative that we develop better prevention, screening, and triaging of patients with ovarian cancers and related tumors. As we understand more and more about ovarian cancer, we're beginning to understand that maybe actually a fallopian tube is the site of origin. And we're also understanding that there may be a distinction between Stage 1 and 2 versus Stage 3. And this is very important in the triaging of patients.

As you heard, there is an unacceptable overall five- to ten-year survival of patients with ovarian cancer-like cancers. The published pivotal studies on the ROMA, in combination with noninvasive preoperative evaluations history, including family history, and, importantly, clinical examination will result in the appropriate referral of patients with pelvic masses scheduled for surgery. And as you saw in the last slide, gynecologic oncologists perform better

optimal cytoreduction and staging of patients.

Published data suggests that referral to a gynecologic oncologist results in a higher percentage of patients being adequately staged and optimally cytoreduced. And optimally cytoreduced means that we remove all visible tumor to less than one centimeter, putting those patients into a better survival. Optimal cytoreduction has been associated with improved disease-free and overall survival in patients with ovarian cancer.

The overall false negative and false positive rates, as reported in the pivotal studies, will improve the triage of patients with pelvic masses to referral centers with gynecologic oncology services. However, importantly, the algorithm, ROMA, is not meant as a stand-alone test, but to be used in combination with clinical examination, a comprehensive history, including family history, and noninvasive radiologic testing, such as CAT scans, transvaginal sonos or MRI.

When used in combination with the clinical findings and radiologic examination, the false negative rate improves. If one evaluates the 17 false negative patients, all of the patients with invasive cancer had either a CAT scan, transvaginal ultrasound, or markedly elevated CA-125 which strongly suggested an ovarian

cancer and would have prompted a referral to a regional center. These patients referred to regional centers would have had optimal care.

Furthermore, if one excludes the low-malignant-potential tumors, or LMP tumors, the false-negative rate is further improved. Based on pathology and molecular markers, the classification of low-malignant-potential tumors should be divided into two categories, serous borderline tumors with noninvasive implants, or SBTs, and serous borderline tumors with invasive implants and micropapillary serous carcinomas. This distinction is very important. The latter category of tumors have a 30 to 40 percent mortality rate and therefore need to be distinguished from the garden variety LMPs that we see, which have almost a 100 percent survival.

In the 17 patients with false negative results, nine are LMPs. Furthermore, our understanding of ovarian cancer now distinguishes Stage 1 and 2 from Stage 3. These are clinically and biologically distinct. The ROMA performs well in distinguishing these stages.

As a practicing clinician, I find this test useful for triaging and regionalizing the care of women with suspected ovarian cancer to high-volume centers

with gynecologic oncology expertise. This referral should result in women undergoing optimal cytoreduction, which, as noted, has been shown to impact survival in this dreaded disease.

I thank you for the opportunity to present these marks before this distinguished Panel. Thank you.

DR. NETTO: Thank you, Dr. Runowicz. The last speaker is Dr. James Orr from the Florida Gynecologic Oncology and Lee Cancer Center.

DR. ORR: Good morning, Mr. Chair, members. Thank you very much for this opportunity, and I will say that the Sponsor is reimbursing me for my expenses and time to be here. My name is Dr. Jimmy Orr, and I'm a board-certified obstetrician/gynecologist, as well as board-certified in gynecologic oncology.

I've been in private practice in Florida since 1985. As a private practitioner, I've been honored to have served as the president of the Society of Gynecologic Oncologists, president of the Florida Society of Gynecologic Oncologists, and have served on the executive committee of the American College of Obstetrics and Gynecology.

Probably related to population demographics, nearly 7 percent of all new ovarian cancers are

diagnosed in my state. My practice is located in a 1,600-bed medical center, and our registry accession's more than 5,000 newly diagnosed patients on a yearly basis. We currently treat more than 150 newly diagnosed ovarian cancers on a yearly basis. So my perspective is given through the eyes of a private practitioner who daily sees women who are self-referred as well as referred by other physicians.

I believe that there are a number of axioms regarding ovarian cancer. Number one, the management of ovarian cancer by trained gynecologic oncologists is associated with decreased morbidity of treatment, increased likelihood of complete staging, and improved survival. Gynecologic oncologists are the only surgical sub-specialists who have the ability to consistently complete the correct procedure with benign intraoperative findings as well as to convert and complete the proper procedure if a malignancy is discovered. Results of a gynecologist combined with any other surgical sub-specialists do not equal the results of a gynecologic oncologist doing this operation alone.

I think these results are very important, specifically in those with early stage disease and tumors of low malignant potential where decisions

regarding extent of surgery and additional therapy, particularly chemotherapy, are absolutely related to the surgical findings. Scientific evidence unmistakably indicates that the correct surgical procedure offers a survival benefit in all women with ovarian malignancy.

In women with an adnexal mass, the ability to accurately predict the presence or absence of a malignancy confers the patient and her family the distinct benefit of appropriate preoperative counseling and preparation and lessens the risk of need for potential reoperation.

Additionally, the ability to obtain this quantitative test that places a woman into a low-risk category should lessen the psychologic stress associated with pre-surgical waiting time. Importantly, low-risk results may increase the use of a minimally invasive approach, lessening overall surgical morbidity in those women who might otherwise be subjected to an open operation.

While every woman with ovarian cancer could benefit from appropriate referral, there are many explanations including but not limited to geographic, economic, and technical reasons why women at risk for ovarian malignancy may or may not be referred to a

gynecologic oncologist for initial or later treatment.

Currently, there exists no clinical, radiologic, or laboratory test used alone or in combination that results in 100 percent positive predictive value for this disease. In this disease process, any objective test that has a one minus NPV or false negative rate of less than 10 percent, when used in the hands of the gynecologic oncologist, should significantly contribute to women's healthcare, remembering that fewer than 50 percent of women with ovarian cancer ever see a gynecologic oncologist.

Additionally, current evidence-based care dictates evaluation and interpolation of the entire clinical situation prior to surgical referral and treatment of that individual patient. Thus, any number of coexisting clinical, medical, or radiologic findings may provoke referral or operation by a gynecologic oncologist even in the presence of a low-risk ROMA.

Importantly, the false positive rate adds little risk to overall care, as these women will be likely referred and operated by a gynecologic oncologist or in a high-volume center where surgical results are typically excellent. Currently, gynecologic oncologists perform seven, that's 2.3 benign and 4.6 malignant, operations on a weekly basis,

as demonstrated by our SGO survey. Thus, the average gynecologic oncologist has additional capacity in their practice to manage those patients who may have a false positive ROMA.

The potential loss of surgical cases referred back by the gynecologic oncologist is small. And, in actuality, after consultation, the patients often prefer to have their procedure completed in a high-volume center.

The results of this pivotal study clearly add an important diagnostic tool for the evaluation and triage of women with an adnexal mass. While individual management should always, and I say always, be guided by the entire clinical scenario, the results from this test should improve women's opportunity to have the correct procedure, lessen their preoperative stress, increase the opportunity to undergo a minimally invasive procedure, and greatly contribute to the future progress of care of those women in this country with ovarian malignancy. And I thank you each for your time.

DR. NETTO: Thank you very much, Dr. Orr. Is there anyone else that would like to speak? We still have a few minutes.

(No response.)

DR. NETTO: Any of the Panel would like to ask questions of the Open Public Hearing speakers?

(No response.)

DR. NETTO: Thank you. We'll proceed now with the agenda. Please note that there will be a second Open Public Session in the afternoon.

We will now proceed to the Sponsor's presentation for the Fujirebio Diagnostics. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. The Sponsor will introduce the speakers, and you will have 60 minutes.

DR. ALLARD: Thank you, Mr. Chairman. Members of the Immunology Device Advisory Panel, members of the Office of In Vitro Diagnostic Devices of the Food and Drug Administration, good morning and thank you for the opportunity to present our data today on a test that we believe represents an important step forward in the treatment of women with ovarian cancer.

I'm Jeff Allard. From 2004 to 2008, I was chief scientific officer at Fujirebio Diagnostics, and during the time I worked at Fujirebio, I was responsible for overseeing the development of the test that you will hear about today. It's called the Risk

of Ovarian Malignancy Algorithm, or ROMA, and it's a tool for assessing the risk of ovarian cancer in women scheduled for surgery for pelvic mass.

First, I'd like to introduce you to Fujirebio Diagnostics, the company that developed the ROMA algorithm. In 1998, Fujirebio, Incorporated, purchased the diagnostics business of Centocor, a company that I'm sure you're familiar with, and formed Fujirebio Diagnostics. Fujirebio Diagnostics develops, manufactures, and sells in vitro diagnostic tests for cancer, and some of their products are listed on this slide.

Now, here is an overview of what you will hear today. Ovarian cancer remains a serious and often fatal disease in women. A number of studies have shown that surgical treatment and survival are substantially improved when women with ovarian cancer are treated by oncologic specialists in high-volume centers. Current methods to discriminate whether a woman with a pelvic mass has ovarian cancer or benign disease are sub-optimal. So this argues for improved tools to estimate the risk of ovarian cancer in women that present with pelvic mass.

And as you'll hear today, ROMA was developed by first evaluating a series of cancer biomarkers

singly and then in combination. Among those tests was HE4. It's a putative protease inhibitor. It is FDA-cleared and has been used and is in use in patients with ovarian cancer for monitoring for recurrence or for progression of disease. Tissue expression of HE4 is restricted primarily to reproductive and respiratory tissues, so it makes a good biomarker.

It's been shown that HE4 is complementary to CA-125 in that it adds sensitivity at fixed levels of specificity. That was how we measured the contribution of HE4 to 125. And we identified that HE4 combined with CA-125 in a logistic model accurately estimated the risk of ovarian cancer in women with a pelvic mass scheduled for surgery. And it provided 89 percent sensitivity at a pre-determined level of specificity of 75 percent. We'll discuss this in more detail in a moment.

This would be the first test cleared by FDA for use by physicians to stratify women with pelvic mass into subgroups of high and low risk of harboring ovarian cancer. It will provide more useful information to ensure the patients are treated by the right surgeon in the right facility and to better plan and implement the most appropriate treatment and postoperative care, as you've heard this morning.

We will present data today that demonstrates that the false negative rate and the false positive rate are both within acceptable limits. ROMA is intended to be used in conjunction with current methods of identifying ovarian cancer risk. These include family history, physical exam, and imaging, as described in various published guidelines, and these are, of course, well known to the members of this Panel. It is also not a tool for detection of or screening for ovarian cancer.

Today, we will demonstrate that the application of HE4 in combination with CA-125 and the ROMA algorithm has the potential to increase the survival of women with ovarian cancer. It may also improve treatment of women with nonmalignant diseases by assisting in the referral of patients to the optimal specialist for their care.

So with these points in mind, here is our agenda for today. Dr. Richard Moore, who is director of the women's program in women's oncology and assistant professor of obstetrics and gynecology at Brown University in Providence, Rhode Island, was the principal investigator on this project. Dr. Moore will describe the current practice for managing women who present with pelvic masses and the unmet medical need

for additional tools to stratify women into high and low risk of having ovarian cancer.

He will be followed by Dr. Steven Skates, assistant professor of medicine at Harvard Medical School and Massachusetts General Hospital. Steve was the biostatistician for this project, and he will describe how the risk of malignancy algorithm was developed.

Then Dr. Moore will return, and he will describe results of the multicenter pivotal trial, and he will specifically address the questions that FDA posed to you.

Finally, I will sum up our presentation, and we look forward to answering your questions. Now I'll turn the podium over to Dr. Moore.

DR. MOORE: Good morning, Mr. Chairman, Panel members. I'm Dr. Richard Moore, and I'm a gynecologic oncologist in the program of women's oncology at Brown University and Woman and Infants' Hospital. I was the PI for this study, and I also work as a consultant with Fujirebio.

I became interested in developing a multiple marker assay for ovarian cancer risk assessment because many of the women in our region were not receiving optimal care for their ovarian cancer. I realized that

we needed a better way to identify women that were at high risk for having ovarian cancer in order to improve their care and increase their survival for this disease. Before I go over the study results, I would like to spend some time examining the unmet medical needs that women with a pelvic mass and ovarian cancer face that can be addressed by a more accurate risk assessment tool, such as a multiple marker assay, or ROMA, the test we'll present here today.

Ovarian cancer remains one of the deadliest of all cancers, and the American Cancer Society estimates there will be approximately 22,000 new ovarian cancer cases each year. And this results in about 15,500 deaths, annually. Ovarian cancer is the number one cause of gynecological cancer deaths and the fifth leading cause of all cancer deaths in women. Unfortunately, ovarian cancer incident rates are either stable or, in some reports, slowly increasing.

The women at highest risk for being diagnosed with ovarian cancer are women that present with a pelvic mass or ovarian cyst. And it's estimated that one in five women will be diagnosed with an ovarian cyst or an adnexal mass at some time in their lifetime. And up to 200,000 women will undergo surgery each year for an ovarian neoplasm. Roughly 13 to 21 percent of

these women will be diagnosed with an invasive epithelial ovarian cancer.

We know that women who are diagnosed with early stage disease are fundamentally curable and that the five-year survival rate for Stage 1 ovarian cancer can reach up to 93 percent. However, the majority of women, more than 70 percent, will have advanced stage ovarian cancer at the time of their diagnosis. And we see the five-year survival rate dramatically decreases to about 40 percent for these patients.

So how can we effect survival for women who will be diagnosed with ovarian cancer? Survival can be increased through prevention, screening, early detection, surgery, and chemotherapy. Unfortunately, we currently do not have effective screening, prevention, and early detection methods readily available to us. However, it has been shown that appropriate surgical management can increase survival for women diagnosed with ovarian cancer, and this is a tool that should be readily available to all of our patients.

So let's contrast the impact of advances in chemotherapy with the impact that surgery can have on patients with ovarian cancer. Over the last 20 years, improved chemotherapy drugs and routes of delivery have

resulted in up to a 16-month improvement in survival. In contrast, comprehensive surgery with optimal tumor debulking and surgical staging performed by gynecological oncologists can increase survival by at least 12 months. With this in mind, we have the ability today, this very moment, to impact positively the survival for thousands of women diagnosed with ovarian cancer just by making sure that these patients have optimal ovarian cancer surgery by surgeons experienced in the management of this disease.

Currently, the best surgical care for ovarian cancer patients is a cytoreductive surgery or for patients with clinical early stage disease to undergo extensive surgical staging. And this will help to define the extent of the disease, determine the need for adjuvant chemotherapy, provide prognosis for the patient, and outline a plan of care.

Studies have also demonstrated that aggressive surgical debulking can improve survival for women with ovarian cancer. So what is an optimal tumor debulking? Well, surgical debulking is a removal of all visible tumor to less than a centimeter in size, and to achieve this, extensive surgical procedures such as bowel resections or diaphragmatic stripping or even splenectomies, in some cases, are performed in order to

achieve the goal of removing all the tumor. These surgeries can be difficult and highly technical and require surgeons that are specially trained and experienced in ovarian cancer debulking.

The surgeons that are trained in ovarian cancer surgery are gynecologic oncologists. And a gynecologic oncologist is a board-certified surgeon that has had four years of training in an obstetrics and gynecology residency and then has gone on for a further three to four years of training in a fellowship of gynecological oncology.

Gynecologic oncologists specialize in the surgical and medical management of ovarian cancer patients. They perform surgery. They administer chemotherapy. And they understand the natural history of ovarian cancer.

In 2007, Goff and her colleagues, in a multi-state study, reported that gynecologic oncologists more often completed a comprehensive cancer surgery when compared with gynecologists or general surgeons. Gynecologic oncologists performed comprehensive surgery twice as frequently as their counterparts. Goff also looked at the outcomes of high-volume surgeons, who are typically gynecologic oncologists, and they found that the high-volume surgeons were more likely to perform a

comprehensive ovarian cancer surgery when compared to low or medium-volume surgeons.

When examining the types of hospitals where ovarian cancer patients had their initial surgery, less than 50 percent of women had their surgery at high-volume hospitals, a hospital where the rate of comprehensive ovarian cancer surgery is the highest. A third of patients had their surgery at low-volume hospitals, where about half of these patients had sub-optimal cancer surgeries.

In another study by Paulsen in the Netherlands, they demonstrated that there is a significant survival advantage for ovarian cancer patients that are operated on by gynecological oncologists when they were compared to patients that had surgeries by gynecologists or general surgeons.

As well, Paulsen looked at where the patients had their surgeries. And patients whose surgeries were performed at tertiary care hospitals versus community hospitals also had a significant survival advantage. In fact, there are many studies both in Europe and in the U.S. with similar findings, demonstrating a survival advantage of up to 18 months for ovarian cancer patients who are operated on by gynecologic oncologists. In a meta-analysis of 53 studies with

over 6,500 patients, it was found that optimal cytoreductive surgery increased survival by up to one year or 50 percent.

So there is no doubt that the type of surgery, the type of surgeon, and the institution where women have their ovarian cancer surgery will improve their survival. Yet, only half of women with ovarian cancer are operated on by high-volume surgeons at high-volume centers, even though the data suggests and demonstrates their survival and outcomes will be improved when they are cared for by multidisciplinary teams and at centers experienced in the care for patients with this disease.

So how do we get the patients to the right surgeons and the right centers, and how do we assess a patient's risk for ovarian cancer? Currently, the tools that are available to us as clinicians for assessing risk of malignancy in women presenting with a pelvic mass include a history, a physical exam, imaging, such as ultrasound and CT scans and MRIs, and sometimes tumor markers, such as CA-125.

The question is: Can these tools be improved to ensure that more women get the right treatment by the right surgeon at the right place? I believe they can, and there is many benefits to an accurate risk

assessment above and beyond triage, which will extend to both the patients and physicians on many levels. For example, a gynecologic oncologist can use the ROMA test in conjunction with referring physicians to increase the number of women with high-risk features that will be operated on by the gynecologic oncologist.

An accurate risk assessment will help the physician plan the surgical approach, such as laparoscopy or robotic surgery for low-risk patients versus laparotomy for high-risk patients. It will help the physician plan for preoperative and postoperative care. For example, a patient with multiple comorbid medical conditions that has a high-risk score, we will now know that more than likely, this patient will need a laparotomy and staging procedure and will allow us to prepare for this patient's care during and after her surgery. Equally important, an accurate risk assessment will enable physicians to better counsel their patients and prepare their patients for surgery.

On the other hand, and more importantly, patients will benefit from an accurate risk assessment, as it will allow the patients to prepare for surgery and develop expectations for their care. They can plan for their care, and it will allow them the selection of the appropriate surgeon and center, and it can relieve

anxiety.

So just imagine in a patient, just imagine the benefits to a woman that has been referred to an oncology center and her expectations are that she has ovarian cancer. Imagine her emotional relief when the physician can sit down with her and say, "Look, you're at low-risk because your score is low, and, therefore, the likelihood that you have ovarian cancer is less than 6 percent."

We have seen that only 50 percent of women with ovarian cancers are operated on by high-volume surgeons or at high-volume centers, and they have improved survival. With a more accurate risk assessment tool, we will enable more ovarian cancer patients to have comprehensive surgeries by oncology specialists at multi-disciplinary institutions that specialize in cancer care. If we can get more of the right patients to the right surgeons in the right hospitals, we can improve survival right now. We don't have to wait for improvements in chemotherapy. We don't have to wait for prevention and screening and early detection. We can take immediate steps today to improve the survival rates for women with this deadly disease. I believe the risk assessment test we will now begin to describe will help us achieve this goal.

And I will turn the podium back over to Dr. Steven Skates, who will explain the test and how it was developed. Thank you for your time.

DR. NETTO: Thank you. If you just excuse me for one second. For the Panel members, the questions will be at the end of the presentation so you can ask all the questions.

DR. SKATES: Good morning, and thank you for the opportunity to describe how and why we developed the risk of a malignancy algorithm, or ROMA. ROMA is a risk assessment tool that I believe can represent a step forward in assessing the risk of ovarian cancer in women with pelvic masses.

I've been working in this field since 1986, and one of the things that I've found most gratifying is the significant impact that statistical modeling can have on the practice of medicine. This impact has yet to be seen in cancer diagnostics. In particular, there is an unmet need in ovarian cancer, which I believe statistical modeling can address.

What's needed is a tool for assessing ovarian cancer risk in women with pelvic masses. We know that CA-125, the tumor marker associated with ovarian cancer, is sub-optimal for this purpose. So we initiated pilot studies to develop a risk assessment

tool for ovarian cancer using statistical modeling of multiple serum tumor markers that would achieve a clinically useful sensitivity and specificity.

To develop this algorithm, we did two pilot studies, a cohort study at Women and Infants' Hospital in Providence, Rhode Island and, importantly, a case control study in Boston at Harvard Medical School Hospitals. The case control study is important because what it does is complement the cohort study and provide a ratio of cases to controls that are approximately 50/50. This is the most allocation for estimating coefficients in statistical models, such as logistic regression, and for assessing the complementarity of additional markers to standard markers like CA-125. This provides the power to make that assessment. That's where the pilot studies come to the fore.

We identified biomarkers complementary to CA-125 by looking at high specificities, such as 90 to 95 to 98 percent, so that we had more signal from the other markers. To validate ROMA, a criterion was set based on clinically acceptable criteria of moderately high specificity, 75 percent.

An independent nationwide prospective pivotal study was conducted. This is a cohort study. The algorithm was developed on the pilot studies, and then

it was then applied to the independent pivotal study and the confidence interval estimated for sensitivity at 75 percent specificity. The question to be addressed by the pivotal study is the following: Does the 95 percent confidence interval for sensitivity lie entirely above the pre-specified clinically acceptable sensitivity?

So the two pilot studies are described in this slide. As you can readily see, the case control study complemented the cohort study so that there are approximately the same number of cases as there were -- are controls when you combine both studies. This gives us a total of 480 patients in the combined pilot studies, with approximately equal cases to controls.

In addition, we know that tumor markers, such as CA-125, differ significantly in their distribution between pre- and post-menopausal women. Therefore, we stratified by menopausal status. In pre-menopausal women, many conditions not associated with ovarian cancer can result in elevations of CA-125. This can confound the interpretation of CA-125 tests and potentially result in false positives. Hence, it is critical that any test that uses CA-125 must stratify by menopausal status. So that's what we did.

In order to achieve both the target high

sensitivity and specificity, we believed we needed a combination of markers, not just one. We assessed 15 candidate tumor markers, including those listed on this slide, all known to be associated with ovarian cancer. We evaluated these 15 candidates, both individually and in every possible combination of panels of size six. And the goal was to find the smallest panel with the highest sensitivity at a given specificity for which additional markers did not significantly increase that sensitivity.

The endpoint in the study was the malignancy status as defined by pathology following surgery on the pelvic masses, which divided the patients between invasive epithelial ovarian cancers and low-malignancy potential borderline tumors from the benign controls.

Here is the distribution of disease type by menopausal status. There are a total of 190 women -- 91 women with epithelial ovarian cancer, 55 of them pre-menopausal and 136 post-menopausal. Fifty-one LMPs, low-malignancy-potential tumors, 17 pre-menopausal, 34 post-menopausal. 236 women with benign disease, 120 pre-menopausal and 16 post-menopausal. Gives a total of 478 women with pelvic masses in these categories, and there were two non-EOC patients not included.

We used logistic regression to evaluate the sensitivity of the combination of biomarkers. And, simply stated, this process is a process of elimination whereby one identifies the best combination of five or six markers and then drops them down one at a time until further removal severely lowers the sensitivity at a given specificity. The goal here is to eliminate in this process any marker that did not significantly improve that sensitivity. And what we found was the minimal subset of biomarkers that significantly increases sensitivity to CA-125 was the combination of HE4 and CA-125.

Any other marker added to this combination did not significantly improve sensitivity. Therefore, based on this selection of biomarkers, the HE4 and CA-125 results, we developed an algorithm that combined these two markers that would estimate the risk of ovarian cancer in women with pelvic masses. We used logistic regression within each strata of menopause and an additional intercept term to allow for the fact that we had case control patients from one of the pilot studies and derived an equation for each menopausal group.

The case control term was then dropped from the equations so that the resulting estimates given by

the equations gave a probability appropriate for a cohort study, which is what the pivotal study is. The result from the logistic regression is a linear model for the index or log odds of having ovarian cancer. The log odds then determine the Risk of Ovarian Malignancy or probability of having ovarian cancer.

These calculations are single-line formulas that can be readily implemented in simple Excel spreadsheets, for example, to provide either the pre-menopausal index, the PI, or the post-menopausal index, also the PI. These formulas don't require complicated computer software nor the associated requirements of distributing and implementing and testing such software. As a result, ROMA can be easily and readily used by any laboratory with a capability of running immunoassays to better identify the risk of ovarian cancer in women with pelvic masses.

The risk of ovarian cancer malignancy algorithm classifies a patient as high-risk if the probability exceeds a given cut point.

ROMA was then validated in our pivotal cohort study. The measure used in the validation criterion is the sensitivity at 75 percent specificity combined over pre-menopausal and post-menopausal groups. It is readily interpreted as the average proportion of cancer

patients with pelvic masses correctly classified as ROMA. That combines over pre- and post-menopausal women in a typical practice which sees pelvic masses and is that -- the sensitivity that results is that proportion.

The validation criterion we set for ROMA in this independent and separate population from the pilot studies in the cohort pivotal study is a minimum of 80 percent sensitivity at a clinically acceptable 75 percent level. Or, more precisely, that the entire 95 percent confidence interval for sensitivity at 75 percent specificity exceeds 80 percent.

Dr. Moore will now describe the prospective multicenter clinical cohort study that was conducted to validate ROMA.

DR. MOORE: Thank you. Well, we know every year in the U.S., somewhere between 100 and 200,000 women will undergo surgery for a pelvic mass, and today we've heard that in order to provide the best care possible for these women, we need better tools to assess the risk for ovarian cancer. I will now talk about how we validate ROMA, a tool that we believe will be beneficial to ovarian cancer patients. And along the way, I will address some of the FDA's questions.

You heard from Dr. Skates how the Risk of

Ovarian Malignancy Algorithm was generated in two pilot studies. We conducted the pivotal trial to validate ROMA. This was a national trial involving a new cohort of patients. And it's important to point out that this cohort did not include any of the patients that were used in the two pilot studies.

The objective of this trial was to validate a predictive model, utilizing HE4 and CA-125, to assess the risk for epithelial ovarian cancer and LMP tumors in women presenting with a pelvic mass. We conducted the study at 14 geographically dispersed centers across the country. And most of the studies had divisions of gynecological oncology and departments of obstetrics and gynecology. This allowed us to enrich the study population with patients with ovarian cancer in order to achieve our statistical power.

This was a prospective double-blind multicenter trial, and all patients were required to be 18 years of age or older. They all had a documented ovarian cancer or pelvic mass with imaging, and they were all planned to have surgical intervention. Patients that were diagnosed with ovarian malignancies in the studies were required to be surgically staged as part of the protocol, and all of the blood samples were obtained preoperatively. We used a central pathology

review to confirm the site pathology diagnosis.

We enrolled 566 patients into the study, of which 530 were evaluable. There were 246 pre-menopausal patients and 284 post-menopausal patients. So now let's look at the pathology distribution of all the cases.

When we examined the disease distribution, we found that 66 percent of patients had benign disease, 24 percent had invasive ovarian cancers, 4 percent had LMP tumors, 1 percent had nonepithelial ovarian cancers, 3 percent had metastatic tumors to the ovary, and 2 percent had other GYN tumors, such as cervical or endometrial cancers.

Similarly, when we examine the patients with benign disease in the study cohort, we see that the spectrum of pathology is what we would typically expect to find in patients with benign pelvic masses or ovarian cysts. For instance, we see that there's a higher incidence of endometriosis in the pre-menopausal patients when we compare them with the post-menopausal patients and there's a higher incidence of serous cyst adenomas in the post-menopausal group when compared to the pre-menopausal group.

When we look at the stage distribution for all invasive epithelial ovarian cancers in the cohort,

this was similar to what we would expect to find in a population of women diagnosed with invasive ovarian cancers. We see that 13 percent of the patients had Stage 1 disease, 14 percent of the patients had Stage 2 disease, 65 percent had Stage 3 disease, 5 percent had Stage 4 disease, and 3 percent were unstaged.

Now let's look at the results of ROMA and the risk stratification into high and low-risk groups. When examining all pre- and post-menopausal women with either benign disease, invasive epithelial ovarian cancers, or LMP tumors, we see that 262 patients with benign disease were classified to the low-risk group, and that 89 patients with benign disease were classified to the high-risk group. And this represented our false positive tests.

When examining women diagnosed with either an invasive epithelial ovarian cancer or an LMP tumor, we found that ROMA classified 134 patients into the high-risk group, and only 17 patients with an invasive epithelial ovarian cancer or LMP tumor were classified to the low-risk group, and these represented our false negative tests.

This provided for a sensitivity of 89 percent at a set specificity of 75 percent and a positive predictive value of 60 percent and a negative

predictive value of 94 percent.

So let's look at the breakdown of the patients with invasive epithelial ovarian cancer and LMP tumors that had false negative tests. We see that in the post-menopausal group, three out of the nine patients actually had LMP tumors and only six patients had invasive epithelial ovarian cancers that had a false negative test. And, therefore, we identified 95 percent of the epithelial ovarian cancers in the post-menopausal group.

In the pre-menopausal group, six out of the eight patients had LMP tumors and only two patients had invasive epithelial ovarian cancers. And these two patients had false negative tests. And, therefore, we were able to identify 89 percent of pre-menopausal patients that had an invasive epithelial ovarian cancer.

When examining all patients together, only 8 out of the 129 patients with an invasive epithelial ovarian cancer had a false negative test. And, therefore, 94 percent of all invasive epithelial ovarian cancers in this trial were correctly identified with ROMA. This is an important finding because over half of the patients with a false negative test had LMP tumors where the clinical effect of a false negative

test is minimal compared to that of a patient with an invasive epithelial ovarian cancer.

When we examined the stratification by stage of invasive epithelial ovarian cancers, we see that ROMA also correctly identifies 86 percent of the Stage 1 and 2 ovarian cancers and nearly all, or 99 percent, of the Stage 3 and 4 ovarian cancers. This is in stark contrast to the historical rate of CA-125, where only half of early stage patients will have an elevated CA-125. And we also know that only about 80 percent of all ovarian cancer patients will have an elevated CA-125.

So let's examine how ROMA performs compared with another risk assessment tool used formally or informally in our clinical practices. The risk of malignancy algorithm, or RMI, developed by Ian Jacobs, is an algorithm that uses the clinicopathological variables to assess risk for ovarian cancers in patients with a pelvic mass. The RMI employs an imaging score, along with CA-125 values, and menopausal status to calculate the risk of malignancy. We compared ROMA to the RMI.

We were able to calculate an RMI using a combination of ultrasounds, CT scans, and MRIs for 80 percent of the study patients. We compared the RMI

values we obtained for ROMA to the results for each individual patient. When we examined benign and invasive epithelial ovarian cancers, we found that at a set specificity of 75 percent, the RMI achieved a sensitivity of 85 percent, compared with ROMA, which had a sensitivity of 94 percent. This difference was statistically significant, with a P-value of 0.01.

When we examined patients with Stage 1 and 2 invasive epithelial ovarian cancers, we found that the RMI achieved a sensitivity of 66 percent compared with a sensitivity of 86 percent for the ROMA. And, again, the difference approached statistical significance, with a P-value of 0.05.

So I've shown you that ROMA correctly identifies 94 percent of all patients with invasive epithelial ovarian cancer and that ROMA alone performs better than the RMI. In addition, ROMA is a simple, easy to use, quantitative test, without the use of subjective data. The ROMA will provide a risk assessment tool that is easy to interpret and we believe will be helpful to physicians in evaluating their patients and beneficial to patients by addressing an unmet medical need we discussed earlier. The ROMA will be a valuable addition to the tools that we currently use to assess risk for cancer.

I would now like to examine the false negative rate for ROMA, which we will show is acceptable. First, the FDA has posed to us a question: What is the clinical tolerable percentage or percentage range of ovarian cancer patients who could reasonably have their initial surgery performed by non-oncology specialists? Expressed in very specific test performance terms, what is the minimal false negative rate, or 1 minus the negative predictive value, for a test assisting in a decision for who performs and initial surgery. Next slide.

The false negative rate, defined by 1 minus the negative predictive value for the pivotal trial is 6 percent when we consider both epithelial ovarian cancers and LMP tumors alone, or together. However, the false negative rate is only 3 percent when we examine invasive epithelial cancers alone. This false negative rate is cut in half because, as we saw earlier, over half of the patients with a false negative test in this trial actually had LMP tumors.

So now let's look at the clinical effect of a false negative test. If we assume that gynecologic oncologists use ROMA to stratify risk and have low-risk patients cared for by non-oncology specialists, then we can to the following calculations. We know there are

22,000 new ovarian cancer cases each year in the U.S., and half, or 11,000, of these patients are currently being operated on by gynecologic oncologists. So when examining patients with either an invasive epithelial ovarian cancer or LMP tumor with a false negative rate of 6 percent, we will see that 660 women will have a false negative test. However, only half of these patients, or 330, will have had an invasive epithelial ovarian cancer. Therefore, potentially, 330 patients with ovarian cancer will have their surgery with a non-oncology specialist.

However, we have to remember that all patients, including those with a false negative test, will actually undergo surgery and therefore will have a definitive diagnosis of their cancer based on the gold standard of pathology. No patients will be left with an undiagnosed cancer as a result of a false negative ROMA test.

For the rare patient that is discovered to have an ovarian cancer in the community setting, some will have their surgeries converted to oncology surgeries, and others will return to the gynecologic oncologist for further care. Even a patient treated by a non-oncology specialist who is already in the gynecological oncology system will be referred back to

the gynecological oncologist for continued management.

Equally important, the ROMA test can be used in addition to other currently available clinical tools, such as history and physical, imaging, and other tools that will assess the patient's risk for malignancy. With this strategy, the false negative rate would be expected to be lower than that for ROMA alone, and, therefore, the data we just presented would be the worst-case scenario.

So with this in mind, we feel that an acceptable false negative rate for ROMA tests would be less than 10 percent when considering both epithelial ovarian cancers and LMP tumors together. The ROMA achieved the false negative rate of 6 percent when we looked at epithelial ovarian cancer cases along with LMP tumors and a false negative rate of 3 percent when we looked at invasive epithelial ovarian cancer patients alone.

Now let's look at the FDA's questions on false positive rates. Is there a maximum percentage of benign disease subjects that would negatively affect or overwhelm an oncology specialist with surgeries that could safely be performed by non-oncology specialists?

Again, expressed in a very specific test performance term, what is the maximum false positive

rate, or 1 minus the positive predictive value, for a test assisting in a decision for who performs initial surgery? Using the definition of 1 minus the positive predictive value as a false positive rate, we see that ROMA algorithm has a rate of 40 percent when examining both pre- and post-menopausal patients together. So the use of this test by gynecological oncologists in the referred population of this study would only decrease the number of benign surgeries they would perform as 75 percent of the benign disease could safely have their surgery performed by non-oncology specialists.

So let's examine again the worst-case scenario where all patients with a pelvic mass are referred and tested with ROMA. As we will show you, the number of benign surgeries potentially being performed by gynecological oncologists would increase minimally. To examine the effect that ROMA had -- the effect the ROMA test could have on the surgical volume for a gynecological oncologist, we used data from the National Institute of Health's consensus statement along with the U.S. population figures and life expectancies for U.S. women and the incident rates for women presenting with a pelvic mass.

With this model, the number of pelvic mass

surgeries performed each year in the U.S. ranged from 105 to 169,000 cases. This number is consistent with published reports. Using an incident rate of 13 percent and the known number of invasive epithelial ovarian cancer cases of 22,000 each year in the U.S., we can calculate there are approximately 169,000 pelvic mass cases each year. We know that the gynecological oncologist operate on half, or 11,000, of the 22,000 ovarian cancer cases. And from our trial, the gynecological oncologist operated on two benign cases for every ovarian cancer, and, therefore, they performed 22,000 cases each year.

If the ROMA test were applied to all 169,000 cases, at a specificity of 75 percent, the gynecological oncologist would now operate on about 37,000 benign cases, an increase of 15,000 cases from 22,000 cases each year. With a sensitivity of 94 percent for epithelial ovarian cancer, almost 21,000 of the 22,000 ovarian cancer cases would now be operated on by a gynecological oncologist, an increase of 10,000 cases a year. The total number of cases the gynecological oncologist would now be required to perform would be approximately 58,000.

Well, let's put this into perspective as to what the potential increase in volume would be for an

individual gynecological oncologist. We know that there's about a thousand gynecological oncologists in the U.S. We see that the maximum number of benign cases would be increased to 37,000 cases each year, representing a maximum increase of 15 cases per gynecological oncologist each year. However, with this, the gynecological oncologist will now capture 21,000 of the 22,000 ovarian cancer cases, significantly raising the number of epithelial ovarian cancers managed by oncology specialists.

The maximum increase in total number of cases for an individual gynecological oncologist would only be 25 cases a year, or two cases per month. This represents a minimal increase in the total number of cases. But, most importantly, this would result in 94 percent of all invasive epithelial ovarian cancers being cared for by oncology specialists.

Based on the worst-case model, as just described, the positive predictive value would be 36 percent, and, therefore, the false positive rate would be 64 percent. And even at this level, gynecological oncologists would not be overwhelmed. And, therefore, even a false positive rate of 64 percent would be acceptable. The false positive rate in the ROMA algorithm in the current study was 40 percent.

So we have shown that ROMA has an acceptable false negative rate and that no patients will be left with an undiagnosed cancer as a result of a false negative ROMA test. In fact, the use of ROMA could substantially increase the number of cancers that are operated on by gynecological oncologists.

We've also seen that the false positive rate is acceptable and that the ROMA will not overburden gynecological oncologists with benign disease. Equally important, it can increase the number of patients with benign disease that can safely have their surgery performed by non-oncology specialists in their community hospitals where they have the support structure and their family.

So, in conclusion, ROMA will assist in providing more accurate risk stratification and providing a tool for physicians to better ensure that the right patients get to the right surgeons in the right hospitals. It will improve the physicians' ability to provide the most appropriate treatments for our patients. And it will help physicians to counsel their patients as to the expectations, anxieties, and management plans for their care. In the meantime, patients with benign disease will be able to safely have surgery in the community hospitals.

I hope you will agree that the ROMA is an appropriate tool to add to our armaterium for assessing preoperative risk for ovarian cancer. Thank you, Mr. Chairman. Thank you to the Panel. I'll turn the podium back to Dr. Allard.

DR. NETTO: Thank you.

DR. ALLARD: I'd like to now summarize what we've heard today. Ovarian cancer remains a significant medical problem with low survival rates. One in every ten women will have surgery for a pelvic mass in their lifetime, and that amounts to more than 150,000 surgeries every year. Published data demonstrate that survival rates can be improved with earlier detection, appropriate therapies, and when women with ovarian cancer have their surgery performed by an oncology specialist at an experienced institution.

And, yet, more than half of American women with ovarian cancer still have their surgery performed by non-oncology specialists in low-volume institutions, while many with benign diseases remain being treated by oncology specialists. So better tools are clearly needed to stratify women with pelvic mass into high and low-risk groups and thereby more appropriately direct their treatment.

We developed such a tool, and it's a test that determines the risk of ovarian cancer in women with a pelvic mass, and we've called this the risk of ovarian cancer -- Risk of Ovarian Malignancy Algorithm, or ROMA. It was developed in two independent pilot studies where we tested 15 different biomarkers. Surprisingly, only HE4 added sensitivity to CA-125 at fixed levels of specificity. So we achieved the goal we set for our study using a simple formula that does not require complex software to operate.

ROMA stratifies risk by menopausal status which is critical for any test that uses CA-125. And I think that's well appreciated by this group. ROMA can be easily and readily used by any laboratory capable of running immunoassays to better identify the risk of ovarian cancer in women with pelvic masses.

The CA-125 HE4 ROMA algorithm was validated in a multicenter prospective double-blind trial of women with pelvic mass scheduled for surgery. ROMA was shown to have 89 percent sensitivity at a pre-determined level of specificity of 75 percent. And that translates into a test that effectively identifies 89 percent of women with ovarian cancer who should be treated by an oncologic specialist. Conversely, it will correctly identify 75 percent of women with a

benign tumor, offering the potential for them to be safely treated by their obstetrician/gynecologist.

Now, the Agency asked you to determine if the false negative rate is acceptable, and we believe we've shown that it is. The ROMA algorithm delivers a false negative rate of 6 percent for all EOC and low-malignant-potential tumors. This is a clinically tolerable percentage for a number of reasons. First, the false negative rate today, the effective false negative rate today, is more than 50 percent. Second, in our trial, over half of the cancer cases stratified to the low-risk subgroup.

As Dr. Moore has shown you, 9 out of 17 in the low-risk subgroup were borderline tumors. And most of the remainder were early stage, Stage 1 and 2. And, lastly, 6 percent represents a worst-case scenario, as some of the cancer cases would have been detected on imaging. Finally, it's important to note that a false negative ROMA result, as Dr. Moore has pointed out, is not a misdiagnosis, but rather, the patient will still undergo surgery by a non-oncology specialist.

We also discussed the false positive rate that FDA asked you to consider. ROMA's false positive rate of 40 percent is also acceptable. And while the number of patients referred to oncologic specialists

will increase with the use of the test, the increase in the number of surgeries is well within the capacity of oncologic specialists to manage. Therefore, the use of the ROMA algorithm will now negatively affect or overwhelm oncology specialists with surgeries that could safely be done by non-oncology specialists.

So, in conclusion, the application of HE4 in combination with CA-125 and the ROMA algorithm has the potential to increase the survival of women with ovarian cancer. It will also improve treatment for women with nonmalignant diseases. This would be the first test of its kind cleared or approved by FDA for this purpose and will help to assure that the 150,000 plus women that have surgery for a pelvic mass each year in the U.S. are treated by the right physician at the right institution.

We thank you for the opportunity to present our data today and, believe it or not, we look forward to your questions.

DR. NETTO: Thank you very much. I would like to thank the Sponsor's representatives for their presentations. And now to the Panel. Does anyone have a question to any of the representatives who presented this morning? Go ahead, Dr. Berry.

DR. BERRY: So, as I understand it, all of

these women would have surgery. The purpose of the ROMA is to appropriately triage them to a gynecologic oncologist if they are likely to have cancer? Is that the point?

DR. ALLARD: That is exactly the point. It is the triage of patients to the appropriate specialist.

DR. BERRY: And you showed data that specialists -- patients who are treated by specialists do better. Why? Is it because they get better chemotherapy? Is it that the specialist knows that they have cancer and does something that's appropriate? Why wouldn't the community physician send them to a specialist if they know that they have cancer?

DR. ALLARD: I'm going to ask Dr. Moore to answer that question. Those answers are well-documented in the literature, and he can explain that quite clearly for you.

DR. MOORE: Thank you for the questions. The reason that patients do better with surgery by gynecological oncologists is that they're specifically trained and know that when we achieve optimal cytoreductive surgeries in these patients, that there is a survival advantage. With a GYN oncologist, we know the natural history of this disease. And as

opposed to general surgeons who sometimes operate on, let's say, pancreatic cancers, and when we operate on pancreatic cancers, doing an optimal cytoreductive surgery really doesn't help what their outcome is going to be. So they don't know the natural history of ovarian cancer, and when they see a patient with ovarian cancer, they often stop and don't proceed on with a radical debulking surgery. As Dr. Orr pointed out, GYN oncologists are really the only surgeons that are specifically trained to take care of oncology patients.

And so that's for patients that present with advance stage disease. Let's talk about patients that present with early stage disease or clinically early stage disease, the patient that comes in with an ovarian cyst that on imaging doesn't look like an ovarian cancer. That is why many of these patients end up staying in their communities. And when these patients have their surgery and on frozen section it turns out that it's a cancer, then surgical staging is very important. And the reason for this is even though at the time of surgery, when we take out a cyst and it's found to be a cancer, and we look around the abdomen and feel and see, and there's no tumor left -- up slide -- slide up, please. Even when we look around

the abdomen and see that there's no tumor left, we know that a significant amount of these patients will actually have advanced stage disease.

So there've been studies where we've looked at patients that have just tumor in the ovary and clinically nothing else. And when those patients are brought back to the operating room and undergo a full surgical staging, which involves peritoneal cytology, it involves lymph node dissections, it involves diaphragmatic pap smears and multiple biopsies, we see that 31 percent of the patients who were thought to be early stage disease are, in fact, upstaged to advanced stage disease of Stage 3C.

So it's very important that people who know the natural history of this disease operate on these patients because GYN oncologists know that if we can get the tumor volume down to less than a centimeter, then that patient is going to have a significant survival advantage, and it's worth doing a radical surgery to get to that point.

And we also know that in patients that have clinically apparently early disease, that many of them, 31 percent, in fact, have Stage 3 disease and need chemotherapy, whereas if they truly have a Stage 1 cancer, they don't need chemotherapy. So that's why

patients do better. It's because the GYN/ONCs are trained and know the natural history of this disease.

DR. BERRY: So just so I understand, the purpose is not to minimize the number of surgeries? They're going to get surgery anyway, is that correct?

DR. MOORE: Correct.

DR. BERRY: Thank you.

DR. MOORE: Thank you.

DR. JASON: Several questions for you. In follow-up to that, a patient who then is found on pathology to have disease comes in then to a gynecology oncologist. How does that affect their outcome as opposed to doing it all at the first surgery?

DR. ALLARD: Yeah, go ahead.

DR. MOORE: Thank you. So, and this happens, unfortunately, on a daily basis, and I'm sure the GYN/ONCs around the country have the same experience that I do. When we have a patient that has been in a community and has a surgery and then on final pathology is diagnosed with ovarian cancer, I guess there are two case scenarios. One could be the case where the cyst was taken out and we think it may be in early stage.

Well, the two routes that that patient can go down is they'll either have a second surgery in order to determine what their surgical stage is to determine

whether they need chemotherapy. And, as I just pointed out, if that patient comes in, she has a 31 percent chance of being upstaged. And that patient will need chemotherapy if they're upstaged. If they don't have any positive nodes or biopsies that are positive and the tumor is confined to the ovary alone, then the surgery is enough as long as they've been surgically staged and are truly a Stage 1 patient.

The other patient that comes in sometimes are patients that have a large amount of tumor, and the surgeon who initially did their surgery either didn't do a attempt at a cytoreductive surgery or couldn't do it. And those patients benefit from having an aggressive attempt at cytoreductive surgery. So, often, these patients will also undergo a second surgery. Or they will undergo chemotherapy. And then we know that their survival rates are not that great compared to patients that have an optimal cytoreductive surgery. So, in many cases, these patients will undergo surgery a second time around or they may get chemotherapy when they really don't need it to benefit.

DR. JASON: Do you have any sense what proportion are in that group?

DR. MOORE: The proportion of?

DR. JASON: The second group you were

describing that have repeated surgery and don't have optimal removal.

DR. MOORE: In Goff's study, they saw that in patients that were operated on by low-volume surgeons, that only half of them had an optimal cytoreductive surgery. So half of the patients wouldn't have a good attempt at having tumor removed.

DR. JASON: Okay. Thank you. A few other questions, but the one that I'm most interested in, when you compared your ROMA, I know you compared it to RMI?

DR. MOORE: Yes.

DR. JASON: In the modeling, did you do two other comparisons, and how did it turn out? One being basically to add the imaging component to your ROMA? Did that have an impact? Did you try it and did that have an impact, specifically in terms of sensitivity? And, secondly, if you were to just take the two tests and say if this person is positive to either, how did that sensitivity compare to what ultimately became the ROMA?

DR. MOORE: Yes, we did those analyses. So I'd first like to bring up the ROMA versus RMI slides with the data showing. So what we did do is we compared RMI and ROMA, and, as I showed you earlier, in

all stages -- up slide -- RMI had -- was less -- had a decreased sensitivity when compared to ROMA. And that was statistically significant. Up slide.

In the Stage 1 and 2 patients, we also saw that ROMA performed better than RMI, and that reached or was near statistical significance, with a 0.05.

The slide that I didn't show you -- up slide -- was we looked at patients that had Stage 1, Stage 2, Stage 3A, which is microscopic tumor outside of the pelvis, Stage 3B, which is tumor of very small volume in size, and Stage 3Cs, where there is no visible tumor in the upper abdomen or in the omentum, but they are Stage 3 based on lymph nodes. So in all of these patients, a CT scan, MRI, or ultrasound would not show disease outside of the pelvis. And, therefore, they would be considered as, you know, either benign or having an early stage, 1 or 2, cancers.

And when we looked at these patients, we saw that the RMI achieved the sensitivity of about 68 percent compared with ROMA, that achieved a sensitivity of 89 percent, and this was statistically significant as well.

So we did take the RMI results -- so all the patients that had a high-risk score on the RMI were

grouped into a high-risk category. And all the patients that also had a high-risk score on the ROMA were also grouped into a category. And then patients that had low-risk scores on both tests were put into one category to see if there was a difference. And when we did this, we did not see a statistical difference between ROMA, sorry, in that population looking at both of them versus ROMA. So, really, the driving factor of the test was the ROMA algorithm for separating these patients into high and low-risk scores.

DR. JASON: Now, here you had mentioned that you really -- you were just barely at significance for some of this. What were your actual sensitivities, although I know you say they aren't significantly different --

DR. MOORE: The --

DR. JASON: -- when you did that.

DR. MOORE: The sensitivities on this were, for ROMA, were 89 percent.

DR. JASON: But the one that you're describing where you did that --

DR. MOORE: They were very similar to 89 percent.

DR. JASON: So they were around the same

place?

DR. MOORE: Yes, they were.

DR. JASON: And then how about if you simply said I'm going to take anyone who's positive to either one of these tests and refer them, never worry -- I'm not going to worry about my false positives? What's your sensitivity in that setting? How did that compare to ROMA?

DR. MOORE: If we took every patient with both tests being positive?

DR. JASON: Either --

UNIDENTIFIED SPEAKER: Either --

DR. JASON: Either one.

DR. MOORE: Yeah, we didn't look at that combination.

DR. JASON: Oh, okay.

DR. MOORE: I'll let Dr. Skates -- he seems to have some information on that.

DR. SKATES: If we could have the slide with the CA-125 and HE5 plot for both the pre-menopausal separately and then the post-menopausal? On the slide, this is the post-menopausal women. And the blue here are the benign disease. The red squares are epithelial late-stage. The pink triangles are epithelial early-stage. And the orange circles are low-malignant-

potential. And you can see the diagonal line that represents ROMA at 75 percent specificity going across there, separating out most of the benign disease from most of the cancers.

And this shows how the diagonal line, which is linear combination of CA-125 and HE4, best separates the controls from the cases. If, in fact, what you're proposing is a straight line, say, at 100 horizontal to the x-axis for HE4 and a vertical line, for example, at 35 for CA-125, then everyone in the upper right quadrant would be positive on that test. But it would be less efficient, less sensitive, in my judgment, by just looking at this than what you would get with the diagonal line.

DR. NETTO: But you did not do this formally --

DR. SKATES: We did not do a formal significant test. I'm just trying to do the best --

DR. NETTO: Okay.

DR. SKATES: -- assessment of this from a plot perspective that I can get right on the spot. And, similarly, on the slide, this the pre-menopausal line, and you can see that if you had in that box a vertical line for CA-125, you would have a lot of false positives for CA-125 that the ROMA doesn't get. There

is a lot of blue below the line. That's mainly because in the pre-menopausal, the weighting is primarily in favor for HE4 because CA-125 has so many false positives in the benigns.

DR. JASON: Okay.

DR. SKATES: And, therefore, it appropriately weights the test in favor of HE4. So what you would get is very -- if you just used HE4 in this situation, you get a similar although not quite as optimal result as ROMA. If you use the combination of CA-125 and HE4, you would get many more false positives.

DR. JASON: So, in terms of the earlier discussion on what is an acceptable amount of false positives, the feeling was this would be beyond what an oncologist, gynecology oncologist could handle?

DR. SKATES: This would decrease the specificity from 75 percent maybe down to 50 percent. And so we would be referring many more, perhaps twice as many to the gynecologic oncologist.

DR. JASON: Um-hum.

DR. SKATES: Whether they could handle that or not is unclear, but we felt that 75 percent specificity and retaining 75 percent of the benigns to the non-oncology specialist was the appropriate minimal level.

DR. JASON: Okay. Okay. Some minor questions. In some of the tables in the primary text, it said that 15 subjects didn't have surgery?

DR. ALLARD: Correct.

DR. JASON: Why didn't they have surgery?

DR. ALLARD: We don't know exactly, but that was a common exclusion, and I'm guessing that because their conditions resolved.

DR. JASON: Okay.

DR. ALLARD: In between the time that they enrolled in the study and the time that their surgery was scheduled.

DR. JASON: Okay.

DR. ALLARD: Oh, I'm sorry. Dr. Moore knows the answer.

DR. MOORE: Yeah, we know that in a small fraction of those patients, they went back for imaging. They had been enrolled. And just before their surgery, they had imaging, and their cyst had resolved, so they were functional cysts.

DR. JASON: Okay. And then it also said 15 subjects were included who didn't meet criteria? Why was that?

DR. ALLARD: Yeah, they were subjects that were enrolled that did not meet inclusion/exclusion

criteria, and the typical ones were things like we found out after they had been enrolled that they in fact had had a previous cancer or that they in fact were on a chemotherapy medication. Most commonly, it was methotrexate. And that would violate one of our exclusion criteria. So it was those kinds of violations of inclusion/exclusion criteria.

DR. JASON: And they were included because it turned out they didn't --

DR. ALLARD: In the additional analysis, we did include those patients because, in fact, they were evaluable.

DR. JASON: I got you.

DR. ALLARD: They were enrolled and they were evaluable.

DR. JASON: Okay. And is the HE4 test licensed already for some use?

DR. ALLARD: Is it licensed?

DR. JASON: Um-hum. For --

DR. ALLARD: To --

DR. JASON: For monitoring?

DR. ALLARD: Ah, it is FDA-cleared for monitoring today, yes, it is.

DR. JASON: Okay. And, lastly, on the labeling, on Page 15, I just want to make sure I

understand this. This has to do with the sensitivity data.

DR. ALLARD: Okay.

DR. JASON: And I don't know this assay, so it's probably something -- I just want to make sure I'm on board. Is this saying that if you have 100 percent increase in concentration, the sensitivity is 31 percent, but if it's only a slight increase, the sensitivity is 71 percent, suggesting that there is ongoing disease?

DR. ALLARD: That's in the discussion on monitoring in the package insert?

DR. JASON: This is in the labeling section of the proposed labeling. There is a table on Page 15, sensitivity represented, risk estimation, blah, blah, blah, and there's a table of percent change in HE4 concentration along with sensitivity and specificity.

DR. MOORE: Yeah, that's in the monitoring package.

DR. JASON: Right.

DR. MOORE: And, typically, how we use serum tumor markers when we're following patients either being treated for ovarian cancer or for following them for recurrences after they've been treated is we look at the trends of their tumor markers. So, for

instance, the most common one that we've historically used is CA-125. I may have a patient that starts with a CA-125 before treatment, 400 or so, and with treatment we reach a baseline of 10. If while we're monitoring them for recurrence we see that goes from 10 to 20 to 35 --

DR. JASON: Oh.

DR. MOORE: -- even if it's still within the normal range, we know that that patient has a recurrence of her disease or most likely by serological. So when we looked at HE4, the same principles applied. So it's more the increase of HE4 that would indicate new disease, and that's where that came from.

DR. JASON: So when you talk about percent change, it's from that very reduced amount, and so you're -- the 100 percent has a lower sensitivity because are you going from a lower baseline or --

DR. MOORE: No. And, you know, I'm not sure where they're going from from that, but what we're looking at is more from the trends over time on tumor marker values.

DR. JASON: Okay. Okay. And the last question is for the assay that was done at three different labs, did you do any quality assessment of

lab variability?

DR. MOORE: I'll let Jeff answer that.

DR. ALLARD: We did. In fact, we ran multiple samples at each of the different laboratories --

DR. JASON: Um-hum.

DR. ALLARD: -- and demonstrated. CVs were always within bounds of less than 10 percent.

DR. JASON: Okay. Great.

DR. ALLARD: In general, the assay has a total CV of less than 7, and that's roughly what we observed at each of the three different laboratories, but there were control samples that were run.

DR. JASON: And do you propose, then, to say that -- well, if they would be -- a given place would be one place anyway. Not to worry. That's good. Thank you.

DR. ALLARD: Okay.

DR. NETTO: Dr. Ozols?

DR. OZOLS: Two questions. This assay, the ROMA test, was used in a very selective population who were referred to cancer centers. In your proposed indication that I read, it is that it -- that this ROMA test be applied to those patients who are referred to a center?

DR. ALLARD: Correct.

DR. OZOLS: So do you see this as not being used by gynecologists in a community? You just want this to be used by patients upon referral?

DR. ALLARD: We have thoughts on that, and I'm going to ask Dr. Moore to answer that as a clinician.

DR. OZOLS: Okay.

DR. MOORE: When we conducted the study, it was mainly in gynecological oncology divisions that were in obstetrics and gynecology, and we did this in order to make sure that we had enough cancers in the study to reach statistical power. We agree with the FDA that the population in this trial is a referred population.

But when we look at our pivotal trial reference patterns and how these patients came to us -- slide up -- we see that about 70 percent of the patients came from gynecologists and about 9 percent from family practitioners and another 9 percent from internists and 10 percent from other sources, such as self-referral or other surgeons.

So we believe that this is a vitally important test for gynecological oncologists to use because it will allow us to do many of the things we

talked about in the presentations, in terms of counseling patients, selecting how we do surgeries, which is very important. We know that it's very important not to rupture a tumor intraoperatively, and if we have a high-risk patient, then maybe laparoscopy isn't the route to go because we often end up rupturing tumors. If we have a high-risk patient and they have multiple comorbid medical conditions -- an 80-year-old with a pelvic mass that has many conditions, such as congestive heart failure, and we have a high-risk test, well, this is going to help us plan for that patient's preoperative and postoperative care. We know that that patient is probably going to end up with a laparotomy, a staging procedure, and be in the ICU, and it's good to know that.

So from a gynecological oncology standpoint, I think this is a vital test for us to have to help manage these patients. Now, if this were used by gynecologists, we feel that the impact on patients would actually be beneficial because many of these patients with cancer would be referred, but we did not study that population.

DR. NETTO: Exactly. So how can you say that?

DR. MOORE: Right. And we didn't study that

population, so we can't extrapolate to that. But where we can use it is in referral, when I have a patient come in for a second opinion and see me, I can thoroughly review their case histories, use ROMA to help me say, okay, you're safe having your surgery --

DR. OZOLS: So but if that patient gets referred to you, you do the ROMA, and even if it's a low malignancy index risk, you're going to send a patient back? I think Dr. Orr said most of those patients are going to stay anyway, right?

DR. MOORE: Yeah, I think that depends on the practice. I know where I am, we have many off-sites, and I actually go out and operate with GYNs on patients that we feel are low-risk, and we currently have our own triage system that we're using. And so patients that are high-risk we keep at our center, and for patients that are low-risk, they can stay on Cape Cod, for instance, which is two hours away from us, and I'll often be in that center on the day seeing patients in the clinic, and if they end up having a cancer, they call me down from clinic. So it will truly help us as GYN oncologists also triage these patients, adequately inform these patients, help with their anxieties. There're many benefits to this test --

DR. OZOLS: Okay. So the second question,

one of your thoughts are about that the risk for malignancy index right now, or some variant of it, is obviously available to every gynecologist that do an ultrasound, do a CA-125, that's standard care, and yet, in that, they had about an 85 percent sensitivity, as you talk about. And, you know, and that's -- so your ROMA test, if we accept it, it's about 89 percent better. The fact is that the majority of patients using this risk malignancy index, which is, you know, not that bad of, say, 85 was borderline -- I mean, possible to range as high as 90 percent, but they're still not referred, right? Only half of the patients are still operated on by physicians who know that they probably have cancer, right? So how do you think this would alter practice just by that change in 8 or 9 percent sensitivity?

DR. MOORE: Well, I think it gives us another tool to assess that. You know, right now, in Europe, they use the RMI formally. In the U.S., some places we use RMI formally, and others, it's a calculation that we do in our head. And we know that ultrasounds are variable. They're subjective. So if you have an ultrasound in a tertiary care center, it's probably going to be a much more detailed ultrasound in terms of looking at architectures of cysts and stuff than what

you would find in the private practice. And that's why the RMI has some subjectivity to it whereas, you know, serum testing and the use of ROMA really doesn't.

When we look at the ACOG referral guidelines -- let's put those slides up -- we see that, right now, ACOG, their guidelines are that patients with a CA-125 of greater than 200 that are pre-menopausal should be referred, or if they have any evidence of, you know, advanced stage disease, ascites, metastasis or a family history. So a lot of the time, these are patients that -- pre-menopausal patients that will be referred in with advance stage disease. And we end up missing early stage disease. And I think that's why half of the patients aren't referred in is just because it does not look like a malignancy when they're looking at imaging and ultrasound results.

DR. NETTO: Just as a follow-up on that. So clarify for us exactly if this test is to be used in a setting where a patient is referred to a gynecologic oncologist? Was the pivotal part done purely in a setting of gynecologic oncologists exactly like the intention to use is or not, because it seems like you keep saying mainly were gynecologic centers, were gynecologic oncologists with experience. So were there some that would have been similar to just a regular

gynecologist getting a patient and did the ROMA? Was the setting of your pivotal part --

DR. MOORE: Yes.

DR. NETTO: Was it purely exactly like the intention to use or not because I'm not so clear on that. It seems to me that it's not. But I would like your opinion.

DR. MOORE: So out of the 14 sites that we had, one of them was a site that had nine gynecologists that are in private practice.

DR. NETTO: And I'm not worried about that.

DR. MOORE: Yeah.

DR. NETTO: The ones that --

DR. MOORE: The remainder of the sites were all divisions of gynecological oncology that enrolled patients onto the trial. So they were all enrolled by GYN oncologists.

DR. NETTO: So everyone was?

DR. MOORE: Yes.

DR. NETTO: So with that being the setting -- but what you just referred to is it may improve this earlier stage pre-menopausal capture of these being referred, but that's not the setting where you studied this test. You cannot make a statement about that. So the ROMA, you didn't do it in an

initial population and showed that it did improve the referral pattern because these are people who were referred not because of the ROMA, were referred because they were thought to have tumor based on the clinical factors, right?

DR. MOORE: Yeah, although --

DR. NETTO: So I don't think we have data to show that the ROMA does capture additionally because they were already boxed in the gynecologic oncology box based on their clinical --

DR. MOORE: Um-hum.

DR. NETTO: -- suspicion, right? And then you did the ROMA as an additional?

DR. MOORE: Yeah, but a point to that, and I agree that it wasn't a referred population, that referred population is already defined as a high-risk population for the fact that they've been referred in. Yet, the ROMA can still stratify patients into high-risk and low-risk very accurately.

And as a GYN oncologist, where we will use that, that will really help me is that phone call that I'll get saying, "Look, I have a patient that has an 8 centimeter cyst. She is 40 years old. And the ultrasound looks like this." And I'll say to my colleague, "I'll be happy to see her. Let's get a ROMA

test on her. We'll have her come in, and that will help us get patients coming in."

You know, we have a very, very close relationship, as most sites do across the country, with the referring physicians or the gynecologists that send patients in, and in collaboration with them as we see their patients, I think this will help us improve that standard of care.

DR. NETTO: But is that the setting you made the study, the pivotal study in?

DR. MOORE: Yes, in our institution, many of those patients came in for second opinions. Some were self-referred in. Some were sent in, as you saw on the pie chart, we showed that GI and internists and family practitioner sent these patients in.

DR. NETTO: But you would agree the misses are the ones that to start with the gynecologic oncologist did not worry about them being cancers, and those we did not study in this --

DR. MOORE: Well, I don't know if that's a 100 percent true, and I think we should bring up the benign disease slide. When we look at the distribution of benign disease in this study and we look at pre-menopausal patients -- let's go down to simple paratubal cysts. Up slide.

So simple paratubal cysts in the pre-menopausal patient, we had 34 of those patients. Well, when we look at paratubal cysts, these are cysts that are balloons filled with water. There is no internal septations, there is no intrapapillary projections, there's no nodules. That is a diagnosis that can be made by ultrasound. Yet, these patients ended up being enrolled on our study. Now, many of them may have been having surgery because they were symptomatic, but we knew in that group that that would be a benign surgery.

For instance, teratomas or dermoids are very well described by MRI. They have a fat component within the cyst. We know those are benign diseases. So there are some patients in this trial that we could have said, yeah, this is benign. You can go back.

DR. NETTO: All right. Thank you.

DR. MOORE: Thank you.

DR. OZOLS: But I want to go back to that hypothetical 40-year-old woman with this 8 centimeter mass, pre-menopausal, okay? She comes in to you and you do the ROMA test, and there's an 11 percent chance that you're incorrect in putting her at low-risk, right?

DR. MOORE: In the -- can you bring up the --

DR. OZOLS: The pre-menopausal. It's, you

know, I think you have 6 percent for --

DR. MOORE: Yes.

DR. OZOLS: And so are you going to say, okay -- is that going to be very reassuring to her that, look, you've got an 11 percent chance of having, you know, a potentially lethal disease, and I'm going to send you back to your gynecologist? I don't think so --

DR. MOORE: Well, I think they have -- you know, these are taken in consultation with all the other clinical equipment that we have in discussions with the patients.

DR. OZOLS: All right. So you're going to operate on her anyway.

DR. MOORE: All of these patients, yes --

DR. OZOLS: -- think she has cancer.

DR. MOORE: All of these patients will have surgery, yes.

DR. OZOLS: Right --

DR. MOORE: That's a requirement. That is a requirement.

DR. OZOLS: But if we use it in a community, then, I mean, this pre-menopausal who has 11 percent risk, you're going to say that's okay, leave her there, and let the GYN guy operate on her? Don't send her to

me?

DR. MOORE: I think that --

DR. OZOLS: If you're wrong 11 percent of the time in a pre-menopausal woman?

DR. MOORE: No, I think when that's compared with what's currently going on, that is a huge improvement. What currently is going on is 50 percent of those patients aren't making it to us anyways.

DR. OZOLS: Right.

DR. MOORE: So it's a huge improvement.

DR. NETTO: Okay. Dr. Freedman?

DR. FREEDMAN: Thank you. To follow up on that question. So you see a patient with a large cyst, pre- or post-menopausal and you're requesting a sample to be tested, but you don't actually see the patient in that scenario? I realize it's a hypothetical, but you don't actually see the patient. So the patient doesn't benefit from the actual correlation of the test findings with the clinical findings by the experts? Is that how you might imagine it would be used?

DR. MOORE: No, and again, we agree with the FDA that this is a referred population. But we can -- you know, often in referral, like they do at many centers, they will set up the test that they want done for when they get there. So CT scans, please order a

CT scan for me and I'll review when the patient gets here --

DR. FREEDMAN: But let's say the ROMA --

DR. MOORE: The same with ROMA.

DR. FREEDMAN: Sorry to interrupt, but let's say the ROMA was in the acceptable benign range. You wouldn't see the patient?

DR. MOORE: No. I think in the way that this trial was set up, it was a referred population. So we would see that patient. And I think there is a lot of benefits to us seeing a patient whether it's benign or malignant. And we can discuss with them many features of ovarian cancer care and risk assessment that maybe the generalist didn't talk about. In my practice, as I had mentioned, we operate at off-site hospitals. And I'll see those patients, and I'll say, well, I think your risk is pretty low. Let's do the surgery on Cape Cod. I'm going to be there anyways. And that way you can be at home in your community where your support structure is. I come down. If it's a cancer, I'm there. We can do a cancer surgery. If it's not, fantastic.

DR. NETTO: But you cannot generalize that scenario.

DR. MOORE: You can to some extent because if

you look at the major teaching -- or the major GYN oncology centers, many of them do it this way. They all have outreach support systems. I know M.D. Anderson does; I know Duke does and UNC. So a lot of these systems operate as regional centers so that they can get the care of gynecological oncologists out to the region.

DR. NETTO: Yes, Dr. Julian?

DR. JULIAN: First of all, as a tertiary care gynecologist for more than 30 years, about three-quarters of the patients I do, benign patients, are redos because they were incompletely or not optimally done. I understand that the training for the average community gynecologist is 12 months of gynecologic surgery as -- generally, okay, in a 48-month residency. The gynecologic oncologist has three to four times this amount of training with much more difficult cases. Now, in terms of the referral of these patients, oftentimes, the gynecologist is not the triage mechanism for these patients. Often, a third party is involved in this.

Now, when I read the material that you submitted, I came at it from a little different perspective. The presentation, which I agree with entirely, gynecologic oncologists should be doing the

cancer, but the question I have is how many of the extremely difficult cases that will be incompletely done, such as the endometriosis here, the ovarian remnants, the tube ovarian abscesses that are misdiagnosed or old, how many of those will not get to a gynecologic oncologist, do you think, because of this? Will this be used as a mechanism to say this is not a gynecologic oncology referral?

DR. MOORE: No, I don't think it should be. I don't think this is a test that is going to be used at that level to stop referrals from going to a GYN oncologist. On the other hand, you know, even if the ROMA test were negative, and we're seeing a patient, and we do a pelvic exam, and it's a fixed in solid mass and we know it's endometriosis, and we know that referring gynecologist is referring her to us not because it's a cancer but just because of the advanced surgical skills, that patient is going to say.

DR. JULIAN: Right. But do you think the third party -- it will never get to you because the ROMA is negative?

DR. MOORE: It's not indicated for that use and that's not what we've tested, so it shouldn't be used that way.

DR. JULIAN: Okay. Is the CA-125 currently

indicated for the triage of these patients?

DR. MOORE: No, it's not. CA-125 has not been cleared or approved for risk stratification of ovarian cancer.

DR. JULIAN: Okay. The other question I have is our first speaker, Ms. Donahue, probably had, by history, either a low-malignant-potential tumor or a germ cell tumor. This test doesn't detect either of those with great specificity, is that correct?

DR. MOORE: Well, we don't know about germ cell tumors. There was probably only two of them in the study, and they're very rare. Low-malignant-potential tumor, it does a reasonable job on identifying LMPs. However, I wouldn't say that she wouldn't have ovarian cancer because I do have a number of patients in this day and age that have early stage and even advanced stage cancers that are living. I have a number of patients that are now 15 years out from their initial diagnosis, have had multiple recurrences. So, you know, there are invasive ovarian cancer patients out there.

And with some of the new information that we're starting to see on the origins of ovarian cancer, as Dr. Runowicz alluded to, the Type 1's and the Type 2's, the Type 1's are probably the ones that progress

on from a benign tumor to an LMP tumor as a pre-cancerous lesion and then into a low-grade tumor, whereas the Type 2s are one that arise sporadically and they're much more aggressive. So there are ovarian cancer patients out there that have been, you know, for a long time survival rates. I appreciate your comments.

DR. FUNKHOUSER: A few questions for you, Dr. Moore. Is the standard of care to stage low-malignant-potential neoplasms?

DR. MOORE: Well, you know, that's a very good question, and I'm not sure that we can say that in this day and age there is a standard of care. Now, in the past, many of the ovarian cancer patients underwent surgical staging, and the main -- or sorry -- LMP patients underwent staging, and the main reason for that is at the time of frozen section, the chances of the final path coming back as invasive ovarian cancer was as high as 20 percent. Now, as we're getting better at pathology and understanding low-malignant-potential tumors, that rate of misclassification on frozen section has dropped down to about 5 percent.

We also have to divide these tumors, the LMP tumors, into serous tumors and mucinous tumors. We know that almost 95 percent of mucinous tumors are

going to be Stage 1. And for many of those tumors, mucinous tumors, we don't stage them any longer, and at Women and Infants', we don't. We get a final pathology for mucinous tumors, we don't go ahead and stage.

Now, for serous LMP tumors, I think the committee is still out on that one. But if you look at the staging rate in this trial on LMP tumor, it was only about 50 percent. And that's because oncologists are now starting to understand that the LMP tumors are not tumors where the benefits -- the patient is going to benefit from a huge debulking surgery, or sorry, they will benefit from a debulking surgery, but knowing their stage is not vital. So patients that will undergo surgery at a community hospital would be referred back into the cancer centers. We'll review their pathology, and if it's truly an LMP tumor, those patients don't undergo further surgical staging, and they don't undergo chemotherapy.

DR. FUNKHOUSER: Next question. If you had a perfect test that allowed you to distinguish op or preoperatively whether a woman with an adnexal mass had a benign serous cyst adenoma, for example, for a serous cyst adenocarcinoma, for example, would you do a different surgical procedure in your approach to that patient?

DR. MOORE: I believe I would. I mean, I think leading up to the surgery is going to be different and how we prepare that patient. You know, for a patient that I think I know has a cancer, they will know the type of surgery they're going to have, a laparotomy with surgical staging and lymph node dissections. A patient that is, you know, let's say they know they have a serous cyst adenoma, well, often, we'll make a Pfannenstiel incision, a much smaller incision, and we'll most of the time, nowadays, we'll use laparoscopy, remove the tumor, put it in a bag, and try and drain the bag intraoperatively and pull everything up through ports or do robotic surgery.

So I think this test will help us in the preoperative setting in determining what the surgery is going to be, how we're going to counsel these patients, and what their postop events will be, in terms of recovery. Are you going to be in the hospital just overnight and have four laparoscopy port sites, or are you going to have a major incision that allows us to do a full surgical staging.

DR. NETTO: So is that based on the ROMA standalone? You will change your approach?

DR. MOORE: Well, he -- no, he asked me a hypothetical question --

DR. NETTO: If you had the test -- yeah, if you had the test and then you went back and talked to --

DR. MOORE: Do you know, I think yes. I would use all those clinical factors in helping us determine how we're going to take care of this patient. So if I have an exam where I have a cyst that's mobile, and it's small enough that I think I can get it into a 10 centimeter laparoscopic bag --

DR. NETTO: But that's not standalone?

DR. MOORE: I beg your pardon?

DR. NETTO: That's not standalone? You're using clinicopathologic, and your analysis did not include that so --

DR. MOORE: Yeah, but --

DR. NETTO: -- you can't say that.

DR. MOORE: There is not a clinical test that I think a physician uses that is the only thing that they use to make a decision.

DR. NETTO: And I'm not arguing with that.

DR. MOORE: Yeah --

DR. NETTO: Actually, I'm arguing for that.

DR. MOORE: Right.

DR. NETTO: But the issue is your analysis did not include any of the radiologic or any of the

other clinicopathologic in term of saying ROMA is better or not, did it have an additive or not benefit to that.

DR. MOORE: Well, we did when we looked at the RMI index, which does use imaging, as well as menopausal status, as well as tumor markers --

DR. NETTO: But in your -- yeah. Okay.

DR. MOORE: Yeah.

DR. NETTO: Next question.

DR. FUNKHOUSER: My next question is if you have a pre-menopausal woman and you've done a Pfannenstiel and you've removed what you think is a serous cyst adenoma and the final path comes back carcinoma, you now refer that patient to a gynecologic oncologist. There is a delay of two to three weeks before she can have a formal laparotomy and formal staging and debulking as necessary. Have we done harm to that patient other than the second general anesthesia and second operation?

DR. MOORE: Well, I would feel that having a second major surgery is unnecessary. And the two routes that these patients can go down when they are referred in is, one, we can talk to them about the risks that they're going to have advanced stage disease and just give them chemotherapy. And some patients

will come and say, "I don't want surgery no matter what," and I'm going to get chemotherapy because all we can do is calculate a risk that they have advanced stage disease. And those patients may get chemotherapy unnecessarily without any benefit. That's a harm. A patient that comes in and has a second surgery, that's a harm. You know, when we can deal with cancer up front and have that patient have their initial surgery that is the correct surgery, that's the most appropriate treatment for an ovarian cancer patient.

DR. FUNKHOUSER: You've argued persuasively that it's a benefit to patients to have operations in local or regional medical centers as opposed to tertiary care center, which may be far distant from their homes. Do you think that the balance is in favor of referral using a screening test or tests to refer them to distant medical centers where they can be seen and managed by a gynecologic oncologist?

DR. MOORE: Again, that's not the population that we studied, but I think if it was used in that fashion, it would pose very minimal harm or risk to that patient and, actually, potentially increase the number of cancers that we're seeing.

DR. NETTO: Dr. Lichtor?

DR. FUNKHOUSER: I have a question for

Dr. Strakes [sic], please?

DR. NETTO: I'm sorry.

DR. FUNKHOUSER: Dr. Strakes, the data that we've been able to see looks at the ROMA test as a standalone test, but, yet, we're given no comparison against CA-125 alone as a screening test. In your opinion, at a level of specificity of 75 percent for detection of LMP or carcinoma of the ovary, is there a statistically significant difference between the ability of ROMA to detect LMP and carcinoma as opposed to CA-125 alone?

DR. SKATES: Yes, in my opinion, there is. That comes from the examination of the pilot study data where we had sufficient cases and therefore sufficient power to make that distinction. In the pivotal study, there is a cohort study, and, therefore, there isn't sufficient power.

If we look at -- slide on, please. If we look at the sensitivity estimates based on a combination of CA-125 and HE4 in the pilot studies that we did, we find that there is a significant increase at a variety of specificity levels, and you can see that with the addition of HE4, that you get significant, both clinically and statistically significant increases in that sensitivity in those combined pilot studies.