

SUMMARY MINUTES

**CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
IMMUNOLOGY DEVICES PANEL**

December 3, 2008

**Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877**

Attendees:**Chairperson**

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CALL TO ORDER

Panel Chairman George J. Netto, M.D., called the meeting to order at 8:30 a.m. He noted the presence of a quorum and that the Panel had received training in FDA device law and regulations.

He stated that the objective for the meeting would be the Panel making a recommendation to the Food and Drug Administration on the 510(k) application K080033 from Fujirebio Diagnostic, Inc.

He described the ROMA, the Risk of Ovarian Malignancy Algorithm, as a mathematical function that used the HE4-EIA in conjunction with the Architect CA-125II assay to create a predictive probability of epithelial ovarian cancer. He also stated its indicated use: for pre-menopausal and post-menopausal women with an adnexal mass who have already been referred to an oncologic specialist and are scheduled for surgery. He then provided a few more details about the application, pointing out that the assay was not indicated as an aid in a decision to proceed to surgery.

He made some general announcements about registration and open public session presentations and then invited the Panel and FDA staff to introduce themselves.

Executive Secretary Dai J. Li, M.D., M.S., Ph.D., after the introductions, made general announcements concerning availability of transcripts, purchasing videos, and providing hard copies of remarks and overheads. He indicated that Mary Long was the press contact for the meeting and made other announcements.

He read into the record the FDA Conflict of Interest Disclosure Statement, and after reiterating the subject of the meeting, the ROMA application, he advised that no conflict of interest waivers had been issued.

He then introduced Dan Bracco as the Industry Representative and read into the record the Open Public Hearing Statement.

OPEN PUBLIC HEARING

April Donahue, an ovarian cancer survivor, indicated that Fujirebio asked her to speak at the meeting and that they were paying her travel expenses.

She described how she was lucky because she had been diagnosed in the early stages of ovarian cancer, which was not the norm, and how an early detection test would help others survive ovarian cancer.

After describing her own plight with getting a correct diagnosis of ovarian cancer, she gave some statistical information, including that only 20 percent of women were diagnosed in the early stages of ovarian cancer.

She then discussed the Goff study regarding symptoms of ovarian cancer, stating that because many of them are misunderstood and vague, the ROMA test was very important.

She then described misperceptions of ovarian cancer diagnostics, and she explained that the current treatments for ovarian cancer were inadequate and that the quality of life was "not wonderful."

She concluded with a discussion of the importance of being referred to a gynecologic oncologist for women in the treatment of ovarian cancer, pointing out that women have a 97 percent chance of having complete surgical staging with a gynecologic oncologist, but as low as a 35 percent chance with a general surgeon.

She ended by stating that as a patient she felt that the ROMA test would be a great tool for women with ovarian cancer.

Carolyn D. Runowicz, M.D., after stating that her travel costs were covered by the Sponsor and that she was receiving an honorarium, explained that she was a gynecologic oncologist and director of the cancer center for the University of Connecticut.

She discussed the need to develop better prevention, screening, and triaging of patients with ovarian cancers and related tumors. The possibility that the fallopian tube was the site of origin for ovarian cancer and that there may be a distinction between Stage 1 and 2 versus Stage 3 were, according to her, both important factors in triaging patients.

She explained that the ROMA test, in combination with a noninvasive preoperative evaluations history, would result in the appropriate referral of patients with pelvic masses scheduled for surgery. She also reminded the Panel that gynecologic oncologists performed better optimal cytoreduction and staging of patients. She further stated that optimal cytoreduction was associated with improved disease-free and overall survival in patients with ovarian cancer.

She discussed that although the overall false negative and false positive rates from the pivotal studies would improve the triage of patients with pelvic masses to referral centers with gynecologic oncology services, the ROMA was not meant as a stand-alone test.

She further discussed how the false negative rate would improve when the ROMA is used in conjunction with clinical findings and radiologic examination. She also stated that if one excluded the low-malignant-potential tumors, the false negative rate would be further improved.

She concluded by restating that she found the ROMA test useful for triaging and regionalizing the care of women with suspected ovarian cancer to high-volume centers with gynecologic oncology expertise.

James W. Orr, Jr., M.D., stated that the Sponsor was reimbursing him for his expenses and time, and he listed his credentials. He then pointed out that 7 percent of all new ovarian cancers are diagnosed in his state, Florida. He also explained that his perspective was given "through the eyes of a private practitioner" who daily saw women who were self-referred as well as referred by other physicians.

He then discussed that the management of ovarian cancer by trained gynecologic oncologists was associated with decreased morbidity of treatment, increased likelihood of complete staging, and improved survival, pointing out that the results of a gynecologist combined with any other surgical sub-specialists did not equal the results of a gynecologic oncologist doing the operation alone.

He also explained that scientific evidence indicated that the correct surgical procedure offers a survival benefit in all women with ovarian malignancy, stating that in women with an adnexal mass, the ability to accurately predict the presence or absence of a malignancy gave the patient the benefit of appropriate preoperative counseling and preparation and lessened the risk of need for potential reoperation. He further stated that the ability to obtain this quantitative test that placed a woman into a low-risk category should lessen the psychological stress associated with pre-surgical waiting time.

Next, he pointed out that any objective test which had a false negative rate of less than 10 percent, when used in the hands of the gynecologic oncologist, should significantly contribute to women's healthcare. He reminded the Panel that fewer than 50 percent of women with ovarian cancer ever see a gynecologic oncologist. He added that the false positive rate added little risk to overall care as those women would be likely referred and operated on by a gynecologic oncologist or in a high-volume center where surgical results were typically excellent.

He discussed that the average gynecologic oncologist performed seven operations per week, which allowed for additional patients who might have a false positive ROMA. He also stated that the potential loss of surgical cases referred back by the gynecologic oncologist was small.

Finally, he reiterated that while individual management should always be guided by the entire clinical scenario, the results from the ROMA test would benefit women with ovarian malignancy in many ways.

SPONSOR PRESENTATION

James Allard, Ph.D., chief scientific officer at Fujirebio Diagnostics, began with a brief history and description of Fujirebio Diagnostics, the company that developed the ROMA algorithm. He described that the company develops, manufactures, and sells in vitro diagnostic tests for cancer.

He gave an overview of the presentation, first describing that there was a need for improved tools to estimate the risk of ovarian cancer in women that presented with a pelvic mass.

He then discussed the development of the ROMA test, stating that it was developed by first evaluating a series of cancer biomarkers singly and then in combination. He explained that among those tests was HE4, an FDA-cleared, putative protease inhibitor used in patients with ovarian cancer for monitoring for recurrence or for progression of disease.

He 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 that it provided 89 percent sensitivity at a pre-determined level of specificity of 75 percent. He also explained that the ROMA 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.

He further stated that the Sponsor would present data that demonstrates that the false negative rate and the false positive rate were both within acceptable limits. He also emphasized that the ROMA test was intended to be used in conjunction with current methods of identifying ovarian cancer risk and was not a detection or screening test for ovarian cancer.

He concluded by describing ROMA's potential in the fight against ovarian cancer and outlined the agenda for the rest of the presentation.

Richard Moore, M.D., FACOG, FACS, the principal investigator for the study and a gynecologic oncologist, first examined the unmet medical need that women with a pelvic mass and ovarian cancer faced, a need which could be addressed by a more accurate risk assessment tool. He pointed out several dismal statistics surrounding ovarian cancer.

He then explained that survival could be increased for women who will be diagnosed with ovarian cancer through prevention, screening, early detection, surgery, and chemotherapy. Unfortunately, he stated, there were not any early detection or screening methods available to women to date. Despite that, he concluded that appropriate surgical management could increase survival for women diagnosed with ovarian cancer and that the ROMA was a tool that helps foster that need.

After contrasting the impact of advances in chemotherapy with the impact that surgery could have on patients with ovarian cancer, he pointed out that the Panel had the ability to impact positively the survival for thousands of women diagnosed with ovarian cancer by ensuring that such patients had optimal ovarian cancer surgery by gynecologic oncologists.

He then described the best surgical care for ovarian cancer patients, that being cytoreductive surgery or, for patients with clinical early stage disease, undergoing extensive surgical staging. He further pointed out that recent studies demonstrated that aggressive surgical debulking could improve survival for women with ovarian cancer and described optimal tumor debulking.

After discussing the role of the gynecologic oncologist in the fight against ovarian cancer, he mentioned the Goff study, stating that it found that gynecologic oncologists more often completed a comprehensive cancer surgery when compared with gynecologists/general surgeons and that high-volume surgeons were more likely to perform a comprehensive ovarian cancer surgery when compared to low or medium-volume surgeons. He also noted that less than 50 percent of women had their surgery at high-volume hospitals.

He then mentioned the Paulsen study, which, like Goff, demonstrated that there was a significant survival advantage for ovarian cancer patients that were operated on by gynecological oncologists when compared to patients that had surgeries by gynecologists or general surgeons. He also stated that patients whose surgeries were performed at tertiary care hospitals versus community hospitals also had a significant survival advantage.

He then explained that the type of surgery, the type of surgeon, and the institution where women had their ovarian cancer surgery would improve their survival, even though only half of women with ovarian cancer were actually operated on by high-volume surgeons at high-volume centers.

He then discussed the current tools used to help get the patients to the right surgeons and the right centers and which help assess a patient's risk for ovarian cancer. He posited that the gynecologic oncologist could use ROMA in conjunction with such tools and with referring physicians to increase the number of women with high-risk features that will be operated on by the gynecologic oncologist.

He also discussed the benefits of an accurate risk assessment, including that it would help the physician plan the surgical approach, such as laparoscopy or robotic surgery for low-risk patients versus laparotomy for high-risk patients, that it would enable physicians to better counsel patients and prepare patients for surgery, and, finally, that it would allow patients to prepare for surgery and develop expectations for their care.

He concluded by stating that with a more accurate risk assessment tool, i.e., the ROMA, more ovarian cancer patients would have comprehensive surgeries by oncology specialists at multi-disciplinary institutions that specialize in cancer care. He emphasized that such a tool could improve survival for women with ovarian cancer today rather than waiting for improvements in chemotherapy or waiting for prevention and screening and early detection tests to be developed.

Steven J. Skates, Ph.D., discussed how and why the risk of a malignancy algorithm, or ROMA, was developed, beginning with a statement about how significant an impact that statistical modeling could have on the practice of medicine and how there was an unmet need in ovarian cancer which statistical modeling could address.

He discussed how pilot studies were initiated 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. He then mentioned the two pilot studies, a cohort study at Women and Infants' Hospital in Providence, Rhode Island, and a case control study in Boston at Harvard Medical School Hospital that were used to develop the algorithm.

He further pointed out that the case control study was important because it complemented the cohort study and provided a ratio of cases to controls that were approximately 50/50.

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

He described that the algorithm was developed on the pilot studies and then applied to the independent pivotal study and the confidence interval estimated for sensitivity at 75 percent specificity.

He then discussed the two pilot studies, mentioning several points, including that any test that uses CA-125 must stratify by menopausal status and in order to achieve both the target high sensitivity and specificity, a combination of markers was needed; in this case 15 were used.

He then discussed other topics, such as the endpoints of the study and the distribution of disease type by menopausal status. He also discussed the use of logistic regression to evaluate the sensitivity of the combination of biomarkers, which found that the minimal subset of biomarkers that significantly increased sensitivity to CA-125 was the combination of HE4 and CA-125.

He further described the development of the algorithm, discussing the use of a case control term, further implementation of logistic regression, and other topics concerning the single-line formula used.

He concluded with a description of how ROMA was validated in the pivotal cohort study, stating that the measure used in the validation criterion was the sensitivity at 75 percent specificity combined over pre-menopausal and post-menopausal groups. He also discussed the validation criterion set for ROMA in that study.

Richard Moore, M.D., FACOG, FACS, discussed the multicenter clinical cohort study that was conducted to validate ROMA, pointing out that the cohort did not include any of the patients that were used in the two pilot studies.

He related the objective of the trial, which was to validate a predictive model using HE4 and CA-125 to assess the risk for epithelial ovarian cancer and LMP tumors in women presenting with a pelvic mass. He also described other details of the trial, including that it was conducted at 14 geographically dispersed centers across the country, that it was a prospective double-blind multicenter trial, and that all patients were required to be 18 years of age or older with documented ovarian cancer or pelvic mass with imaging who all planned to have surgical intervention. Other details of the trial were also described.

He discussed the pathology distribution of all the cases, including disease distribution, patients with benign disease, and stage distribution for all invasive epithelial ovarian cancers in the cohort. He then examined the results of ROMA and the risk stratification into high and low-risk groups and covered false positive and negative results as well.

He then described the breakdown of the patients with invasive epithelial ovarian cancer and LMP tumors that had false negative tests, stating that 95 percent of the epithelial ovarian cancers in the post-menopausal group and 89 percent in the pre-menopausal group were in fact identified. He further stated that 94 percent of all invasive epithelial ovarian cancers in the trial were correctly identified with ROMA.

Next, he discussed stratification by stage of invasive epithelial ovarian cancers, noting that ROMA also correctly identified 86 percent of the Stage 1 and 2 ovarian cancers and 99 percent of the Stage 3 and 4 ovarian cancers.

He then covered how ROMA performed compared to the RMI and reiterated the many benefits of the ROMA test, emphasizing that it would be a valuable addition to the tools currently used to assess risk for cancer.

He examined again the false negative rate, framing his discussion around a specific FDA question, and ultimately stated that no patients would be left with an undiagnosed cancer as a result of a false negative ROMA test. In the same manner, he then examined the false positive rate, again framing his discussion around specific FDA questions, ultimately stating that the false positive rate was acceptable and that the ROMA would not overburden gynecological oncologists with benign disease.

Finally, he concluded with a brief summary of the benefits of the ROMA test as a tool for assessing preoperative risk for ovarian cancer.

Dr. Allard summarized the Sponsor's presentation, reiterating several points, including that ovarian cancer remained a significant medical problem with low survival rates and that better tools were needed to stratify women with pelvic mass into high and low-risk groups and thereby more appropriately direct their treatment.

He then described the ROMA test again, reiterating that it was a test that determines the risk of ovarian cancer in women with a pelvic mass and one that stratified risk by menopausal status.

He also briefly summarized both the two pilot studies that developed ROMA and the multicenter cohort study that validated ROMA.

He stated that the false negative rate was acceptable, noting that a false negative ROMA result was not a misdiagnosis, but rather, the patient would still undergo surgery by a non-oncology specialist. He also stated that the false positive rate of 40 percent was acceptable.

He concluded with a statement that the application of HE4 in combination with CA-125 and the ROMA algorithm had the potential to increase the survival of women with ovarian cancer.

Q&A

During a lengthy question and answer session, Panel members questioned the Sponsor.

First, there was discussion about why patients who were treated by

specialists had a better outcome. There was also discussion about how patients who were found on pathology to have disease and then came to a gynecology oncologist are affected in terms of their outcome. During this discussion, Dr. Moore described and discussed two different case scenarios.

Other topics were also covered, including comparisons with ROMA and a lengthy discussion on the ROMA versus the RMI test. Inclusion/exclusion was briefly addressed, as well as quality assessment of lab variability.

There were concerns about whether the ROMA would be used by gynecologists in a community rather than just upon referral, as the indication reads. There was also discussion about how the ROMA would alter practice just by a change in 8 or 9 percent sensitivity from the RMI, which was already being used.

Another topic covered was whether the pivotal part of the study was done in a setting of gynecologic oncologists exactly like the intention to use. This led to more follow-up questions concerning the referred population.

Questions also arose about whether the ROMA detects germ cell or LMP tumors with great specificity as well as whether the standard of care is to stage low-malignant-potential neoplasms. Hypothetical scenarios involving surgical approaches were also pondered, and whether or not the ROMA was a standalone test was discussed.

After discussing other points briefly, a lengthy conversation ensued regarding whether there was a statistically significant difference between the ability of ROMA to detect LMP and carcinoma as opposed to CA-125 alone.

Finally, confusion about how ROMA could really change the management of the patients was addressed, followed by a lengthy discussion regarding concerns about the false negative rates and if the ROMA fostered a new pathway to "reverse referrals."

FDA PRESENTATION

James P. Reeves, Ph.D., gave a description/analysis of the FDA questions to the Panel. He stated that the major clinical question was whose clinical services would give the best clinical outcome based on the likelihood of benign versus malignant disease. He also noted that the need for oncologist resources in performing the surgery might still be an open question.

He then discussed the ROMA's proposed new intended use and indications for use, pointing out that the FDA was seeking the Panel's advice concerning the suitability of the definition of the intended use population for the test as it would be used in practice, as well as the Panel's advice concerning the safety and effectiveness of the algorithm regarding this clinical impact.

He stated that, in many situations, diagnostic tests should be considered in the total clinical context, but the evaluation of the manner in which test results could be safely and effectively combined with other clinical

pathologic data had not been carried out for ROMA. Therefore, the FDA was seeking the Panel's advice concerning whether and how the results of the ROMA could be safely and effectively combined with other information.

He then addressed the analytical performance characteristics of ROMA, including variability in the predictive index.

He concluded with a lengthy discussion on the pivotal study design, ultimately asking the Panel to comment on the reliability of general methods of menopausal status determination and if specific instructions were needed to ensure safe and effective use of the ROMA algorithm.

Marina V. Kondratovich, Ph.D., provided a statistical analysis for the FDA. She began with an introduction that commented on the intended use population subjects in the clinical study, pointing out that for certain groups of subjects, the performance of the ROMA test was not known.

She then discussed the fact that while the assumption was that the ROMA test would be used in conjunction with other clinical findings in patients with pelvic mass who were referred to an oncology center and scheduled for surgery, there was no ancillary pre-surgical information that was provided for evaluation besides or in combination with test results. She therefore presented data that looked at ROMA as a standalone test.

She described that ROMA was developed using a training set. She discussed such topics as cutoffs for defining low risk and high risk, sensitivity and specificity estimates, and variability.

After that, she went into the performance of the ROMA test as a standalone test, discussing pre-menopausal and post-menopausal subjects and using a ROC curve to display her findings. This analysis concluded that among 100 pre-menopausal subjects who were already referred to oncology specialists but were defined by the ROMA test as a low-risk subject, approximately 5 subjects had LMP or epithelial ovarian cancer.

She then presented a series of tables and graphs, including ones that displayed detailed information about sensitivity of the ROMA test for the pre-menopausal subjects, ROMA values for the post-menopausal subjects, data regarding 270 post-menopausal subjects and how the ROMA test performed for those subjects, more detailed information about sensitivity, and more detailed information regarding the performance of the ROMA test.

She also discussed several other topics, including the ROMA as a qualitative test, during which she emphasized that clinical interpretation of the performance of the ROMA test for the data combined in such a way depended on the proportion of pre-menopausal and post-menopausal patients in the study.

Next, she analyzed the performance of the ROMA test versus CA-125 alone versus HE4 alone for pre- and post-menopausal subjects with LMP and epithelial ovarian cancer, noting that the data of the clinical study did not demonstrate that there was a statistically significant contribution of the HE4 test beyond the CA-125 in the combination ROMA for either group.

She then considered the performance of the ROMA test versus CA-125

alone versus HE4 alone for patients with Stages 1 and 2 of epithelial ovarian cancer, ultimately stating that, given the small sample size, there was no statistically significant improvement in sensitivity of the combination of CA-125 and HE4 for both pre- and post-menopausal patients with Stage 1 and 2. She then presented analysis on the ROMA versus RMI versus CA-125 alone.

She concluded with a brief summary of her presentation.

Robert L. Becker, Jr., M.D., Ph.D., discussed clinical issues. He began with an introduction in which he pointed out the need for improved laboratory testing to help distinguish ovarian cancer from benign pelvic or adnexal pathology. He also discussed how one could use any diagnostic test in general safely and effectively. He then provided a brief examination of some studies of CA-125 as an ovarian cancer marker in the adult female general population.

He discussed the strategies employed in designing the ROMA test, such as the adding of HE4 for use along with CA-125 and changing the intended use population. He also pointed out that different conclusions were drawn by the Sponsor and the FDA as to the significance of the HE4 contribution in the ROMA model, explaining further that the FDA did not find evidence for independent contribution by HE4 with the size of the study as performed.

He also considered the patients in Fujirebio's study, noting that they were not a general screening population, having been chosen in part to increase the prevalence of disease. He further discussed the intended use population in terms of its specification: women going to surgery after referral for pelvic mass. Other topics were included in this discussion, including patients not included in the study and other circumstances for presentation and treatment of patients.

He then described the two reasons why assertions about test performance were best confined to the test's use in patients like the ones studied: the likelihood that the prevalence of diseases, whether malignant or benign, varied substantially across studied and unstudied patient groups, and the spectrum of disease varied across the populations. He also discussed other topics, including variation in sensitivity and specificity. He discussed an FDA question which concerned the congruence of the studied population with the intended use population and suitable labeling for the test.

Next, he discussed the effects of the choice of the population enrolled in the Fujirebio study: A strong clinical truth (the surgical and pathological findings) was assured for virtually all patients enrolled, and Fujirebio set conditions where the prevalence of cancer was increased many fold.

He also discussed the variation of sensitivity, noting another FDA question that regarded whether ROMA had sufficient sensitivity and negative predictive value for safe use in the pre-menopausal and post-menopausal intended use populations. He then considered test-driven departure from current patterns of practice at oncology centers in assessing safe use of the test.

He explained the ways in which the practical impact of the ROMA test might be better understood. First, he stated one should understand ROMA performance in the context of other clinical pathologic information. Here, he

pointed to another FDA question that asked for the Panel's assessment about how the new test might be knowledgeably used in conjunction with other tests. Second, he stated one should examine ways of mitigating the effect of miscalls. Here, he pointed to the FDA question regarding whether the harm was significantly different for relatively common miscalls among LMP or low-stage patients than it was for less common miscalls among high-stage cancer patients.

During this discussion, he also examined pathways to such mitigation and pointed to another FDA question regarding the practicality and benefit of an intraoperative conversion approach to mitigating the effect of false negative test results in the intended use population.

His last topic of discussion, which reflected another area of FDA's concern, regarded the determination of menopausal status for women who will receive the test. Speaking for the FDA, he then asked the Panel's opinion about methods for assessing menopausal status and about any need for standardization of such methods when used as part of ROMA.

He concluded with a brief statement regarding the six FDA questions posed to the Panel and noted that the second question was "surely the most important of them all."

Q&A AND PANEL DISCUSSION

During another lengthy question and answer session, several concerns were addressed by both the FDA and the Sponsor.

A main concern regarded the difference in the interpretation of the statistical analysis by the Sponsor and the FDA. During this discussion, the Sponsor noted that even though they were comparing ROMA to CA-125, CA-125 was never cleared or approved by FDA for the purpose that ROMA was intended for. The Sponsor also emphasized that HE4 was selected not just based on the improvement and sensitivity at fixed specificities, but also because it addressed the limitations/flaws of CA-125. Cutoffs, the use of biomarkers, and probability were also mentioned in this discussion.

The Sponsor then provided a comparison/contrast between the two different statistical analyses, addressing reasons why the FDA analysis was not valid and dealing with some confusion about the data. Lack of power, appropriate specificity, cut points, the delta method, and the bootstrap approach were also covered.

The FDA then noted the importance of the question of whether, as used, the ROMA test actually separated cancer from non-cancer patients, and further discussion ensued.

Other questions raised concerned the appropriateness of adding HE4 in the post-menopausal group, whether the FDA had considered asking an endocrinology opinion on the selection of the endpoint for FSH level, and how much effect the reclassification of pre- and post-menopausal had on the results of the study.

Lengthy discussion followed in which comments were made on FSH

testing and the confounding effect it could have if women were not classified (pre/post-menopausal) correctly. The FDA ultimately pointed out that their main concern was that if there were other means by which menopausal status might be determined by a wide variety of practitioners in a wide variety of settings, would there be a risk that there could be a drift in the performance of the test and/or would the wrong equation be used as a result of misclassification?

Other concerns were addressed, including some regarding the indication, the definition of a pelvic mass, whether the Sponsor had data that supported that their populations of patients were comparable to what other centers were seeing, and whether the Sponsor collected patient histories on original CA-125 levels.

Concerns about the utility of the test in terms of the intended population were also addressed, and a discussion on the labeling ensued. The likelihood of the ROMA test being used off-label, issues with LMP tumors and the benefit of ROMA, as well as more discussion on the danger of reverse referrals and the confusion surrounding the intended use were also discussed at length. Other topics covered were issues with imaging compared with ROMA and concerns with the pre-menopausal subset.

OPEN PUBLIC HEARING

Robert C. Knapp, M.D., introduced himself and provided brief background in which he mentioned that he was a co-developer of the CA-125. He also expressed his excitement to see the improvement over CA-125 in the new ROMA test.

He briefly described the ROMA, pointing out that it was a significant improvement over reporting just a number (as with CA-125). He also explained that the HE4/CA-125 assay would be more accurate than the CA-125 assay in evaluating an adnexal mass in pre-menopausal women.

Next, he discussed the importance of evaluating all parameters in determining whether a mass was benign or malignant, emphasizing that the HE4/CA-125 assay was only part of the decision-making process in the evaluation of the adnexal mass.

Finally, he mentioned an article he wrote in the journal *Gynecologic Oncology* and concluded with a "wholehearted" endorsement of the HE4/CA-125 algorithm as a significant advance in the fight against ovarian cancer.

Cara Tenenbaum, J.D., M.B.A., on behalf of the Ovarian Cancer National Alliance, described the Alliance, noting its objective to increase awareness of ovarian cancer and describing its work in advocating for federal resources to support research that would lead to more effective diagnostic tools and treatment for ovarian cancer.

She then explained that although the Alliance received some funding from pharmaceutical and biotechnology companies, including Fujirebio, they have a strict policy that fundraising efforts do not affect their policy work. She also mentioned that the Alliance did not endorse any specific device, drug, or therapy

for ovarian cancer.

She also discussed an Alliance survey conducted in 2007. She described the general results of the survey and then continued with a discussion in which she reminded the Panel that the majority of women with ovarian cancer continued to be diagnosed in Stages 3 or 4 when survival rates are low. The key reason for that, she explained, was that a valid and reliable early detection test did not exist for ovarian cancer.

She then shared some personal stories from the respondents of the survey of delays that prevented an early diagnosis. These stories backed up her assertion that early and comprehensive testing for ovarian cancer remained a critical need and that women were largely unaware of the existence of gynecologic oncologists.

Next, she discussed the importance of correct diagnoses and referral to gynecologic oncologists. She also pointed out that the improvement in the accuracy of any risk stratification device could encourage testing among general practitioners who may be reluctant to use methods that have limited accuracy, such as the CA-125.

She concluded by asking the Panel to think about the risk to women for using the ROMA test and how that compares to the risk of not using the test. She also urged them to consider, even though the Sponsor was not requesting it, if the test was only approved for use by GYN oncologists, not front-line doctors, how that would help women.

David A. Fishman, M.D., gave a brief introduction in which he stated that the Sponsor was covering his travel expenses. He explained that his perspective was as a gynecologic oncologist who "takes care of patients." He emphasized the fact that any tool that would help identify women with ovarian cancer and that would have them referred to and be treated by a gynecologic oncologist has been proven to save lives, decrease morbidity and pain and suffering.

He then described what gynecologic oncologists were, pointing out that they were the only board-certified surgeons in the world who were trained experts in dealing with treatment and diagnosis of women with gynecologic malignancies.

Next, he discussed how women's healthcare is compromised when they are operated on by non-gynecologic oncologists and, therefore, optimizing patient triage was a critical step to saving women's lives. He also addressed the topics of reverse referral and intraoperative frozen analysis.

Finally, he concluded by reiterating that the bottom line was that he wanted to optimize patient care and that there were no good tools available. He ultimately stated that, as a gynecologic oncologist, he believed ROMA was a tool that would help.

SUMMATION

Dr. Allard stated that Fujirebio remains committed to bringing better diagnostics to bear on "this awful disease." **Dr. Moore** stated that survival is improved for women with ovarian cancer whose surgical care is managed by a

gynecological oncologist, and ROMA would more accurately identify women with pelvic masses at risk for ovarian cancer.

PANEL DELIBERATIONS AND FDA QUESTIONS

The Panel proceeded with deliberations regarding the FDA questions.

Dr. Reeves read Question 1 to the Panel:

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

- (a) Does the population accrued to the pivotal study adequately match the population and indications described in the Sponsor's proposed intended use?
- (b) Is the proposed intended use sufficiently clear and appropriately crafted to prevent ill-advised use of the test beyond its stated indications?
- (c) If "no," how can this be remedied in labeling or through obtaining additional data?

The Panel members gave their answers and opinions. During this time, several concerns were discussed further, including the confusion of the intended use. To prevent the concern over the intended use among Panel members, it was stated that the intended use would benefit from adding a negative sentence.

Issues with labeling, such as its vagueness and how limitations and warnings should be stated, were also discussed further as there was still concern that the intended use population was not clear enough. Concern that ROMA was going to be used in an ill-advised manner was also brought up, and the Panel discussed obtaining additional data from the Sponsor to remedy that.

Some other concerns were also noted, including that the current stated indications were too narrow and that wording should be added to clearly state that it was not studied in the setting of primary care.

Chairman Netto then summarized the Panel's general consensus. He said that, generally speaking, the Panel felt that ROMA's current intended use was not sufficiently clear and to prevent ill-advised use, the Panel suggested that they build in some parameters.

He stated that the Panel had three suggestions. Because they felt that the sentence, "Subjects categorized as low-risk of cancer using the ROMA value may have surgical intervention performed by a non-oncology specialist," might be a little suggestive and might lead to reverse referral, they therefore advised the FDA to delete it. Second, they suggested that the "scheduled for surgery" language be changed and replaced with "candidates for surgery." Lastly, the Panel suggested that the FDA either insert a sentence in the limitations or intended use section that indicated that ROMA has not been tested in the general population setting and

was not intended for use in that setting.

Some Panel members also recommended that more data be collected.

Dr. Reeves, after getting clarification on the three suggestions above, thanked the Panel.

He then read Question 2 to the Panel:

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

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

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

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

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

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

The Panel members gave their answers and opinions. During this time, some concerns were discussed further, including whether or not ROMA was really safe for the women to be operated on by a non-oncology specialist. The lack of data to say that ROMA was safe and effective if that surgery is done by a non-oncologist was a key issue. Some questions and concerns regarding the statistical analysis were also further discussed, and the issue of reverse referral was again raised by those Panel members who felt that no test should be used to refer people back into the community.

There were also concerns raised about triaging patients. Some Panel members felt that it was more appropriate to give the patient the data and then let them decide on a plan of action; in other words, to use ROMA as a patient management tool rather than a triage system. Others felt that an effective triage system would be useful and that the goal should be to get the patients to a GYN oncologist; however, they also felt that ROMA should be further tested in a trial.

Chairman Netto then summarized for the FDA. He stated that

regarding 2(a), the Panel felt that ROMA did not prove that it was an adequate test in terms of for whom surgical intervention performed by a non-oncology specialist is appropriate.

With the answer of no for (a), he then addressed (c), stating that, in addition to the remedies suggested for Question 1 (taking the sentence out of the intended use and inserting that there is no data on the primary), the Panel felt that obtaining additional data in the primary population would help.

With regards to (d) and (e), there was controversy concerning the actual question where some Panel members felt it was a "bad question" and others stated that once the warnings were made in (a) and (c), it made it unnecessary to address (d) and (e) because patients were already getting the best care they could possibly get. Panel members were also generally hesitant to give the FDA a "percentage" as was requested by Dr. Reeves.

Steve I. Gutman, M.D., M.B.A., from OIVD, then interjected, urging the Panel to let the FDA know whether they felt that a labeling fix would make ROMA safe and effective or whether they thought that more data was needed in order to be safe and effective.

After further discussion prompted by this question, the Panel seemed to feel that additional data was needed rather than just labeling, but this was not unanimous. Some Panel members supported a labeling remedy but still felt that how safe ROMA needed to be was a difficult question to answer without another study. Question 2(d) and (e) were not completely answered as they were generally felt to be irrelevant.

Dr. Reeves read Question 3 into the record:

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

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

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

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

The Panel members gave their answers and opinions. There was brief discussion regarding (a), and **Chairman Netto** quickly summarized that the

Panel members generally felt that the answer was no as far as availability of data to correlate with the clinicopathologic data and that that was why the test was studied as a standalone.

There was then discussion on (c) in which some Panel members expressed a need for more data on secondary objectives as more data would solve the discomfort that they felt regarding approving it as a standalone test. There was also further discussion on the need for more data versus just a change in labeling.

Chairman Netto then summarized that the general consensus of the Panel was that more data was needed in terms of the covariance clinicopathologic collection of data and that it should await clearance until that data is collected because it might give the suggestion that ROMA was a standalone test. He also reiterated one of the Panel's primary concerns, that being their inability to enforce the use of ROMA in the primary care setting and that approval could potentially open another door for using it as a standalone test by primary care physicians in deciding who goes to an oncologist and who does not.

Dr. Reeves again thanked the Panel, and he then read Question 4:

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

The Panel deliberated briefly over this question, giving their answers and opinions. Most of their concern surrounded the fact that because the early stage of ovarian cancer was a critical area, as those are the patients that survive best if properly treated, monitored, and managed, it was imperative to correctly assign low-stage tumors.

Chairman Netto summarized that the general consensus of the Panel was that the LMP issue was "arguable" but that mis-assigning a low-stage was not any less significant than mis-assigning a high-stage because it is an opportune time to catch ovarian cancer as it made a significant difference in patients' lives if caught at low-stage versus high-stage.

Dr. Reeves again thanked the Panel, and he then read Question 5:

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

The Panel deliberated briefly over this question, giving their answers and opinions. Most members deferred to the gynecologic oncologists on the Panel. The significant difference between gynecologist/general surgeon

versus the gynecologic oncologist and how important the gynecologic oncologist's expertise was in the surgical realm was mentioned. Also discussed was the impact on the patient/physician relationship and the many negative factors that could come into play with an unprepared patient. Furthermore, it was expressed that, in most cases, when a malignant tumor was unexpectedly found, a gynecologic oncologist would not be "hanging around the corner ready to jump in the OR."

Chairman Netto summarized this discussion, stating that the general feeling of the Panel members was that it did have a serious medical impact and that it was something to avoid. The only exception would be in a setting where a gynecologic oncologist was on standby, but the general feeling was that that would not be a common situation.

Dr. Reeves read Question 6 to the Panel:

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

The Panel gave their opinions and answers. During the discussion, some mentioned that a reasonable definition that was accepted should be stated somewhere in the literature that is going to be provided. On the other hand, some felt that they did not want FSHs added to the assay as it might complicate things further. Still others felt it had a huge impact on the model, and there were also comments that advisement from endocrinology experts as to whether it would be appropriate to use the FSH and how to use it would be a good idea.

Chairman Netto summarized the Panel's answers and opinions, stating that they generally felt that, as a basic premise, it was acceptable the way it was listed. He added that if the FDA felt that they needed the consultation from an endocrinologist regarding the effectiveness of one-time FSH at the intra-laboratory variation to put something in the wording, they would leave it up to them.

Dr. Reeves thanked the Panel.

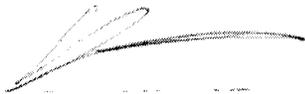
Chairman Netto then asked for further comment or question. No reply was given. The meeting was then adjourned.

I certify that I attended this meeting on December 3, 2008 and that these minutes accurately reflect what transpired.



Dai J. Li, M.D., M.S., Ph.D.
Designated Federal Officer

I approve the minutes of this meeting as recorded in this summary.



George J. Netto, M.D.
Chairman

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