Questions

1) The proposed intended use population is “premenopausal 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 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?

2) 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 (n=504, excluding the 28 cancer patients whose tumors that were not epithelial ovarian):

			95% Confidence Interval	
Patients	Parameter	Observed	Lower Bound	Upper Bound
Premenopausal	Sensitivity	76.5%	60.0%	87.6%
Premenopausal	NPV	94.9%	91.6%	97.3%
Postmenopausal	Sensitivity	92.4%	86.3%	96.0%
Postmenopausal	NPV	92.6%	87.3%	96.0%
All	Sensitivity	88.9%	82.9%	93.0%
All	NPV	93.9%	90.9%	96.1%

    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)?

3) The pivotal study presents no data or analysis of interaction between Predictive Probability (ROMA) results and other clinicopathologic variables (e.g., patient's symptoms, physical findings, imaging) for detecting the presence of ovarian malignancy. Therefore, no formal demonstration is possible that use of the test together with clinicopathologic data is clinically beneficial.

   a. Given the pivotal study data, can clinicians knowledgably 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 sponsor address this in labeling or through obtaining additional data?

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.

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

6) Sponsor performed re-determinations of menopausal status for 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 postmenopausal were reclassified as premenopausal. 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 sponsor's test?