

# Novel Markers Trial: Screening Summary

Updated 28 March 2012

## 1. Study Aims

Our primary goal is to assess the safety, feasibility, and positive predictive value (PPV) of two alternative epithelial ovarian cancer (EOC) screening strategies. Our translational goals are first to demonstrate an acceptable strategy for EOC risk assessment and screening, and second, to provide the preliminary data needed to implement screening if ongoing trials show a mortality reduction, or for a new efficacy trial if ongoing trial results are promising but not definitive. In this trial we aim to:

1. compare referrals for surgical consult, protocol indicated and additional surgical procedures, significant lesions identified, and PPV between the two screening protocols. We will follow each woman for at least 2.5 and up to 4.5 years, and expect about 93 surgeries and 10 malignancies to be identified in this population by the end of calendar year 2013. The experimental strategy (Arm 1) uses CA125 and HE4 as a first-line screen to select women for imaging. Because both CA125 and HE4 exhibit greater variability among women than within a woman over time, the parametric empirical Bayes (PEB) longitudinal algorithm can improve lead time. The PEB interprets rise in a marker as a signal of disease. If one or more equally promising new markers emerges prior to or during the period of the study, those markers will be measured and, if evidence is sufficiently compelling, added to the first-line screen.
2. compare compliance with primary screens, secondary screens, and surgical referrals between the two screening protocols.
3. compare the two screening strategies in terms of potentially adverse effects including changes in health-related quality of life (HRQOL), cancer worry and symptom reporting. We will measure HRQOL at baseline and follow up, and assess effects based on an intent-to-treat analysis. Cancer worry (and symptoms reporting as an objective measure of cancer worry) will be assessed in all participants prior to each screening visit and will be monitored during the period of the trial.

## 2. Eligibility Requirements

### 2.1. Inclusion Criteria.

Women are potentially eligible if they meet the criteria to qualify for one of the following risk groups:

Risk Group 1 (High Risk): BRCA Mutation carrier – Women ages 25 - 80:

- 1a. The subject has tested positive for a deleterious germ line mutation in BRCA1 or BRCA2.\* *\*women with a suspected deleterious mutation are also eligible to participate in risk group 1*

Risk Group 2 (High Risk): Significant pedigree – Women ages 35 – 80. Pedigree conditions can be satisfied by multiple primary cancers in the same person.

- 2a. The subject has a personal history of breast cancer diagnosed before or at age 50.
- 2b. OR the subject has a personal history of bilateral breast cancer
- 2c. OR the subject has one first-degree relative with breast cancer diagnosed before or at age 50.
- 2d. OR the subject has two breast cancers in the first or second degree relatives, same lineage, with at least one breast cancer diagnosed before or at age 50.
- 2e. OR the subject has three or more first or second degree relatives, same lineage, with breast cancer diagnosed at any age.
- 2f. OR The family contains at least one ovarian cancer diagnosed at any age in the first or second degree relatives.
- 2g. OR the subject is of Ashkenazi ancestry and has had breast cancer diagnosed at any age.
- 2h. OR The subject is of Ashkenazi Jewish ethnicity and has one first or second degree relative with breast cancer diagnosed at any age (must be in the same lineage as the Ashkenazi ancestry)
- 2i. OR The subject has a male relative with breast cancer diagnosed at any age
- 2j. OR The subject has a personal history of a positive genetic test result for a deleterious germline mutation in the P53 gene.
- 2k. OR The subject has tested positive for a deleterious germline mutation in one of the DNA mismatch repair (MMR) genes associated with the Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC, also known as Lynch Syndrome) The MMR genes include MLH1, MSH2, MSH6 and PMS2.
- 2l. OR the subject has a first or second degree relative with an identified deleterious germline BRCA1 or BRCA2 mutation, but has not yet undergone testing herself.
- 2m. OR the subject has a first or second degree relative with an identified deleterious germline MMR gene mutation, but has not yet undergone testing herself.
- 2n. OR Probability of carrying a BRCA1 or BRCA2 mutation given family pedigree of breast and ovarian cancers exceeds 20% by any existing BRCA mutational probability model.

Risk Group 3 (Otherwise elevated risk): OvCaRisk model – Women ages 45 - 80:

- 3a. Have measurement of CA125, HE4, MMP7 or Mesothelin exceeding the 95th percentile;
- 3b. OR have a relative risk of at least 2 based on the EpiRisk logistic regression model including age, family history, and other risk factors.

## **2.2. Exclusion Criteria**

Women are ineligible to participate if any of the following are true:

- 1. Removal of both ovaries for any reason.
- 2. History of ovarian, fallopian tube cancer or peritoneal carcinomatosis.
- 3. Currently pregnant.
- 4. Unable or unwilling to provide informed consent.
- 5. Unwilling to provide the name of a physician.
- 6. Unwilling to sign informed consent and/or medical records release form.
- 7. Current untreated malignancy (other than non-melanoma skin cancer).

8. Currently receiving adjuvant chemotherapy or radiation therapy for cancer (except tamoxifen or aromatase inhibitors +/- lupron). Patients who are being treated may enroll 3 months after completion of last treatment.  
*-women who have been diagnosed with recurrent or metastatic disease who are not currently undergoing chemo or radiation but are likely to go back on such treatments during the course of the study should not be enrolled.*
9. Intraperitoneal surgery within the last 3 months (laparoscopy or laparotomy).
10. A medical condition that would place subject at risk as a result of the blood donation, including but not limited to bleeding disorders, chronic infectious disease, emphysema or serious anemia.
11. Subject has a family member who is a carrier of a BRCA or MMR gene mutation and the subject has undergone genetic testing that included the family mutation and no mutation was found, and there are no cases of ovarian cancer in the family.

### **3.0 Screening Overview**

Two screening protocols will be compared, as shown in Figure 1. The protocols differ in the tests used in their first- and second-line screens. In both arms, a blood test will be used as a first-line periodic screen to select women for referral to a second-line screen. In both arms, the Parametric Empirical Bayes (PEB) longitudinal algorithm will be used to tailor marker thresholds to the individual woman. The PEB determines the expected value of a marker for each individual woman based on her menopause status and marker history. Screening will be risk-based so that women with a documented mutation or significant pedigree will be screened semi-annually with early recall at 3 months. The remaining women will be screened annually with early recall at 6 months.

At each screen, women with normal results will be asked to return for the same periodic screening (6 months for risk groups 1 and 2; 12 months for risk group 3). Thresholds for CA125 and HE4 positivity will be set such that 10% of participants are expected to be asked to return for early recall at each screen of whom 100% (Arm 1) and 50% (Arm 2) are asked to come in as soon as possible for a repeat test as outlined below. We estimate that approximately 1.4% of women will be referred back to their primary care physician at each screen with recommendation for clinical follow-up based on abnormal blood and/or imaging results. Clinical follow-up will be coordinated by the study oncologist(s).

Frequency of screening is determined by the participant's assigned risk group. The risk strata are listed above in Section 1.0. A woman is classified as belonging to the highest risk group to which she qualifies. Groups 1 and 2 (high risk) will be offered semi-annual screening while participants in group 3 will be screened annually.

#### **3.1. Cost of Screening and Other Study Activities**

Items with an asterisk below are provided by Coordinating Center at Fred Hutchinson; the cost for all other activities will be provided by your institution.

### Participant Contact

Study mailings (recruitment, screening reminders, results)  
Phone calls (recruitment, follow up, results)

### Data Collection

Study tracking and questionnaire entry database\*  
Questionnaire data entry

### Blood Draw

Blood Collection Kit: 10ml SST vacutainer tubes, 1 10ml EDTA vacutainer tube, 15 pre-labeled 1.5 ml microcentrifuge tubes  
Phlebotomy  
Processing and Storage

*Women in risk groups 1 and 2 have 2 regular screens per year. Women in risk group 3 have 1 regular screen per year.*

*Arm 1: 10% will have elevated primary screen and require a follow-up (confirmatory) screen. Women will be referred for TVUS if one or both markers are elevated at the follow-up screen, followed by a recommendation for early recall screening at 3 months for risk groups 1 & 2, and 6 months for risk group 3. Women with a normal follow-up screen will return to regular screening: every 6 months for risk groups 1 and 2, every 12 months for risk group 3.*

*Arm 2: 5% will have elevated primary screen and require a follow-up screen. 5% will be slightly elevated after the primary screen and require just early recall. Women will be referred for TVUS if one or both markers are elevated at the follow-up screen, followed by a recommendation for early recall screening at 3 months for risk groups 1 & 2, and 6 months for risk group 3. Women with a normal follow-up screen will return to regular screening.*

### Measurement of CA125 and HE4

Weekly batched shipping of one 1ml serum aliquot/draw to FHCRC for testing.  
CA125 assay\*  
HE4 assay\*  
Any additional experimental marker assays\*

Please note that protocol-indicated assays must be performed at the Coordinating Center and cannot be billed to insurance or serve as a patient's clinical test of record. In that same vein, clinical CA125 or HE4 test results may not be substituted for protocol-indicated testing.

### Protocol Indicated TVUS

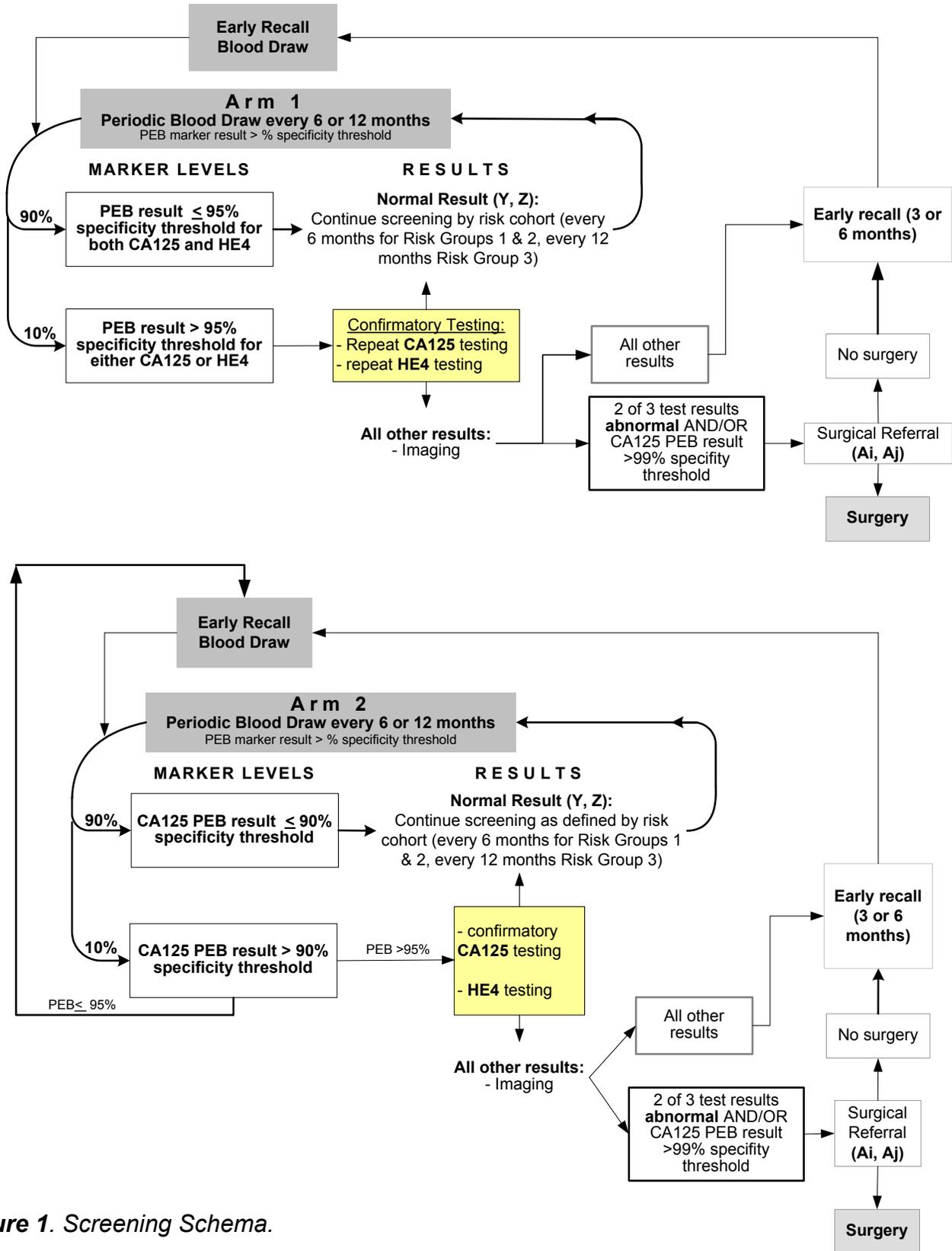
~7-8% participants will require one TVUS following an elevated confirmatory screen. If TVUS was performed within 3 months prior to the elevated screen those results may be used instead of having the participant undergo another ultrasound.

### Surgical Collections

If a participant undergoes bilateral salpingo-oophorectomy (BSO) during the trial sites are required to collect one blood sample drawn as close as possible to the time of surgery and to either have in place a IRB-approved protocol to collect and bank tissue samples from the

surgery for research purposes, or make sure access to tissue blocks and slides is available to study researchers upon request.

**Novel Markers Trial Study Schema: Screening Overview**



**Figure 1. Screening Schema.**