

# Ovarian Cancer Early Detection Biomarkers Trials and Regulatory Issues

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# Topics

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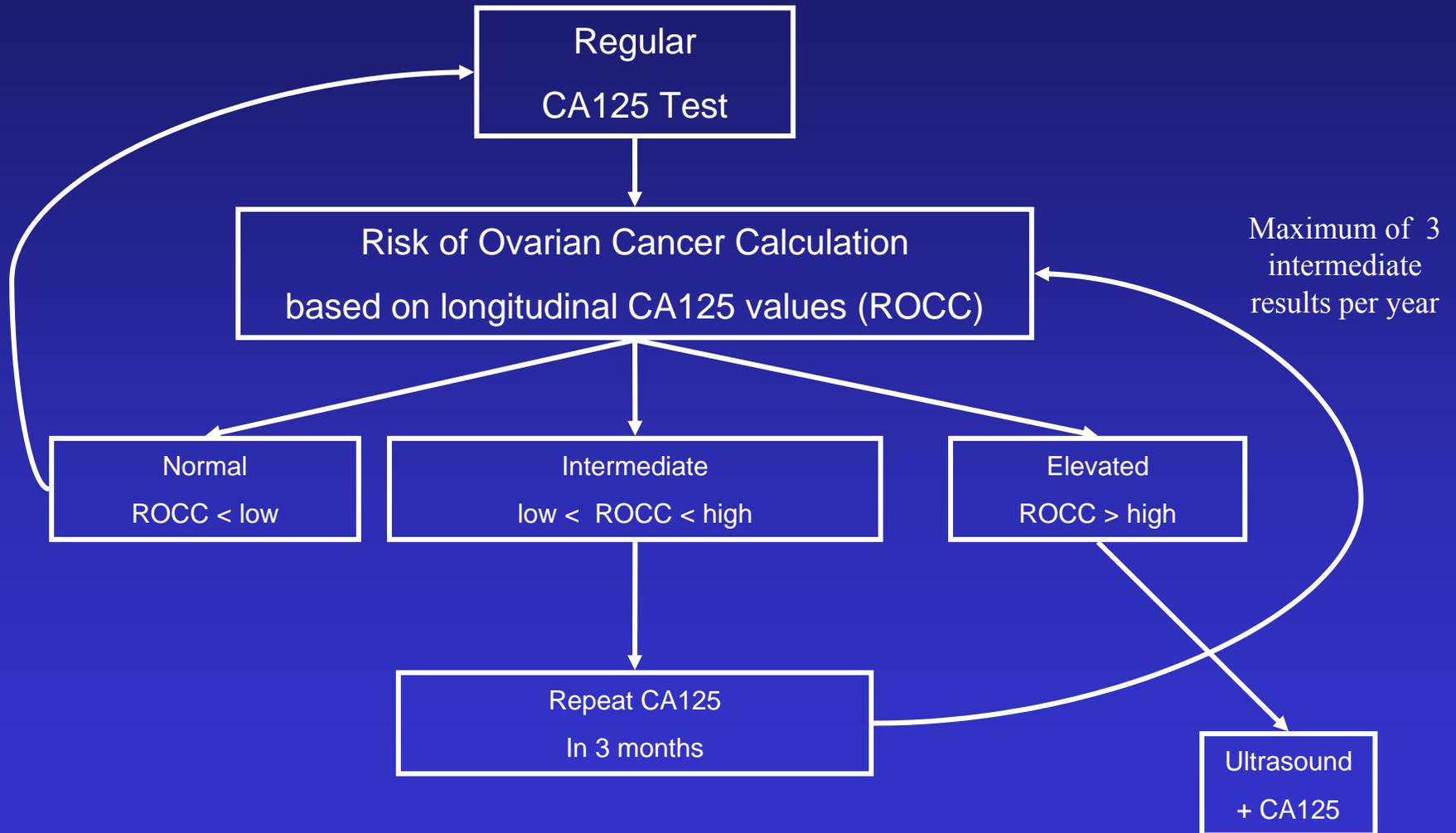
- Update on Ovarian Cancer Markers
- The EDRN/SPORE/PLCO project
- Formulation of a Claim
- Key Questions
- Anticipated levels of regulatory/IP complexity
- Discussion

## Marker Updates—Ca 125

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- Approved marker to test for recurrence
- Remains the single most sensitive and specific marker for ovarian cancer to date
- Addition of other markers might improve sensitivity and specificity
- Longitudinal assessment may also improve sensitivity and specificity.

# ROCA: Risk of Ovarian Cancer Algorithm

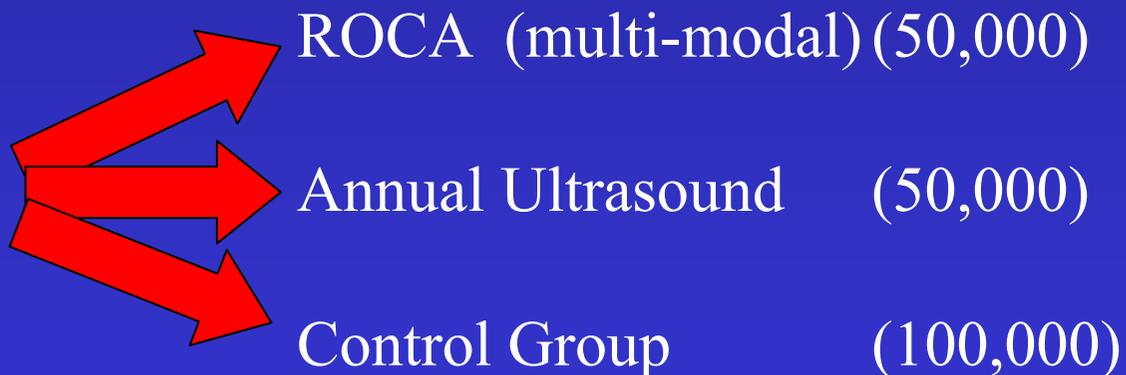


# UKCTOCS: UK Collaborative Trial of Ovarian Cancer Screening

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Principal Investigator: Ian Jacobs MD  
Menon, Skates, Parmar, Fallowfield, Campbell

200,000+ post-menopausal women have been accrued (Sep 2005) & randomized to three arms. Annual screening for at least 6 years, and at least one year of additional follow-up.



Funding: MRC, NHS-R&D, ICRF, CRC

# Marker Updates—OvaCheck

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- In 2002, a paper in Lancet described an approach to ovarian cancer screening using mass spectrometry to create protein patterns from blood and computer software to find patterns associated with disease.
- In 2003, the software developer announced it would market a test called OvaCheck for screening high risk populations. The test would be offered as a “homebrew” diagnostic circumventing the need for pre-market review.
- In July 2004, the FDA ruled that the computer software was, in fact, a medical device and would require review.
- In 2004 and 2005, the developer announces partnerships with several hospitals to further validate the assay and patents “A process for distinguishing between biological states based upon hidden patterns from biological data.”

# Marker Updates—CIPHERGEN Panel

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- Collaborating with several academic centers, CIPHERGEN has sought to combine mass spectrometry with Protein Chip arrays including some antibody-based chips.
- In 2004, a paper in Cancer Research identified three biomarkers: Apolipoprotein A1 and transthyretin (both down-regulated), and a fragment of inter- $\alpha$ -trypsin (up-regulated) in ovarian cancer. The three markers plus CA 125 had a sensitivity of 74% for early stage disease and specificity of 97%. An update in 2006 CEBP, found somewhat lower sensitivity and specificity when benign disease included. Testing is underway on a panel of 7 markers.

# Marker Updates—Yale's Panel

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- In a paper in PNAS in 2004, a group led by Yale investigators used antibody microarrays to identify four proteins that distinguished ovarian cancer: leptin, prolactin, osteopontin, and insulin-like growth factor II.
- The combination had a sensitivity of 95% and specificity of 95% for distinguishing ovarian cancer, all stages.
- In 2006, Yale announced it would partner with a Chinese diagnostics company to develop this panel as a screening test for ovarian cancer.

# Marker Updates—Luminex Panel

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- In an AACR abstract, Lokshin et al from the Univ. of Pittsburgh used the “bead-based” Luminex system for multiplexing many antibody-based assays to distinguish ovarian cancer cases from controls.
- Eight biomarkers had the highest diagnostic power including: CA 125, CA 19-9, EGFR, G-CSF, Eotaxin, IL-2r, cVCAM, and MIF.
- For postmenopausal ovarian cancer the sensitivity was 100% at a specificity of 98.6%.
- Has partnered with Pittsburgh biostatisticians to develop an algorithm to combine the markers.

# Marker Updates— SPORE, EDRN, PLCO Collaboration

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In 2005, leaders of the Prostate, Lung, Colon, and Ovarian Cancer (PLCO) screening trial announced they would accept applications for use of PLCO serum specimens. Dan Cramer representing ovary for EDRN and Nicole Urban representing the Ovarian SPORES agree to submit a joint proposal to identify the current “best” panel of ovarian cancer markers in a “pre-validation” set of case-control specimens and then apply that panel to the pre-diagnostic specimens from the PLCO screening trial.

# Sites and Principal Investigators

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Brigham and Women's Hospital PI: Daniel Cramer, MD.

Fred Hutchinson Cancer Research Center PI: Nicole Urban, ScD

Fox Chase Cancer Center PI: Andrew Godwin, PhD

MD Anderson Medical Center PI: Robert Bast, MD.

University of Alabama, Birmingham

PI's: E. Partridge, MD. & Bill Grizzle, MD., PhD.

Univ. of Pittsburgh Cancer Institute PI: Anna Lokshin, PhD

# PLCO Consultants

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- Christine Berg, Richard Hayes, and Patricia Hartge, PLCO Trial
- Sandra Buys, Univ. of Utah School of Medicine

# Background

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- General population screening for ovarian cancer requires a sensitive, specific, and low-cost approach such as one or more serum-based markers.
- 20+ putative biomarkers have been evaluated by SPORE and EDRN investigators using standard ELISA assays, bead-based (Luminex) assays, as well as the SELDI Panel.
- Following a pre-validation step using case-control samples from EDRN/SPORE sites to identify a “consensus” panel, the PLCO will provide pre-clinical specimens from women who developed ovarian cancer yielding Phase III (i.e. prospective) validation.

# Hypothesis

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A panel of biomarkers will have better performance characteristics as a screening test for pre-clinical ovarian cancer than any single marker, and yield a longer lead time than CA125 alone.

# Pre-Validation Sample Set

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- The pre-validation sample assembled by SPORE and EDRN investigators includes:
  - 160 cancer cases including 80 early stage (Stage I or II) and 80 late stage cases (bloods drawn pre-operatively)
  - 160 benign controls (adenomyosis, endometriosis, fibroids, and benign ovarian neoplasms)
  - 480 healthy controls
  - 40 healthy women from whom serum samples were obtained one year apart
  - 40 premenopausal cases and 80 controls
  - Replicates of a serum pool to assess assay variability

# Aliquots for the Pre-Validation Study

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- Two ml of sera is available for each subject in the pre-validation set.
- Each two ml aliquot will be separated into 4 aliquots to go to four assays sites. Original IDs on the specimens will be re-coded to be blinded when they are returned to the assay sites.
- The sets will be blocked to include an admixture of cases, benign disease controls, healthy controls, serial samples, and replicates to minimize confounding due to assay batch differences.

# Laboratory studies for Pre-validation Assays

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- MGH will receive 1ml of serum and perform standard platform based (Roche E170) assays including CA 125, CA 19,9, CA 72.4, CA15.3, CEA and plate based assays from Fujirebio, DiaDexus, DSL, and Quidel including HE4, SMRP, IGF2, B7-H4, DcR3, and CCHI3L1.
- Fred Hutchinson will receive 0.5 ml and perform single-plex Luminex bead assays including SLPI, Spondin, Cadherin 6, and antibodies to CA125, HE4, and SMRP and Spondin.

# Laboratory studies for Pre-validation Assays

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- Pittsburgh will receive 0.3 ml ml and perform multiplexed-bead Luminex assays including: Prolactin, MIF, TSH, IGF-BP, Eotaxin, CYFRA21.1, sVCAM-1, MMP-2, EGFR, Leptin, GH, and several cytokines.
- MD Anderson will receive 0.2ml and perform the Protein Chip-based assays including Hepcidin, ITIH4, B2-microglobulin, transferrin, transthyretinin, and apolipoprotein A1.

# Selecting a Consensus Panel

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- Logistic regression analysis will be used to form a composite marker (CM) defining a panel's sensitivity at 95% specificity.
- Goal is to achieve at least 90% sensitivity at 95% specificity for the combined early- and late-stage cases in the Pre-validation test set.
- The individual assay's performance based on coefficient of variation will also be considered.

## Phase III Study Using the PLCO Specimens

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- By summer of 2007, we will have identified a working consensus panel as well as extended Luminex panels of biomarkers to be assessed in the PLCO specimens. We will present our final plan to the PLCO leadership for use of their specimens.
- We will request that pre-clinical specimens for all women diagnosed with ovarian cancer in the PLCO, diagnosed at screening or during follow up, be pulled as well as controls who did not develop ovarian cancer during followup.

# Phase III Validation

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- We will use a phased approach to analysis of the PLCO specimens with the baseline specimens and specimens obtained within the year prior to diagnosis tested first.
- Controls will be women who did not develop ovarian cancer during the period of follow up and will be matched to cases by age and storage time of the specimen.
- PLCO has requested that a minimum of serum be used. The amount we request will depend upon number of markers in the consensus panel, reliability of the Luminex or SELDI assays and availability of alternative standard ELISAs that don't require excessive volume.

# Sample Size Considerations

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- With 100 cases, the 95% confidence interval will have width  $\pm 6\%$  to  $\pm 8\%$  for sensitivities between 80% to 90%.
- In cancer screening, it is important to achieve a minimum positive predictive value (PPV), or proportion of screen indicated surgeries at which the target cancer is found, since we must seek to minimize invasive diagnostic procedures done where no cancer is found.
- A control to case sample size of 10:1 would ensure the study has sufficient power to rule out a PPV of 10% or less, that is, less than 9 false positive surgeries for every true positive surgery.

# Key Questions

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- Can an existing serum repository that collected data prospectively prior to a cancer outcome be used as part of regulatory proceedings to support at least a pre-market application regarding use of biomarkers for the early detection of ovarian cancer?
- Must a formal protocol be submitted to the FDA prior to the analysis of the prospective data which clearly states the “claim” and establishes parameters for the “trial.”
- Must the testing be conducted at a CLIA-certified laboratory with assay(s) meeting GMP standards.
- What is the nature of the “claim?”

# Possible Clinical Claims

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- We propose the following marker(s), ....., predict(s) a chance of at least (e.g. 70%) that a woman will develop ovarian cancer in the next (e.g. two) years with a false positive rate no greater than (e.g. 30%).
- We propose the following marker(s), ....., combined with secondary imaging predict(s) the chance that ovarian cancer will be found at the time of pelvic surgery is (e.g. 80%).

## Less Likely Claims from PLCO Data

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- We propose that the following marker(s), ....., will be able to distinguish a benign from a malignant pelvic mass with a certainty of (e.g. 90%).
- We propose that the following marker(s), ....., will be able to predict with a (e.g. 70%) likelihood that a marker-positive tumor has recurred.

# Levels of Complexity

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- I. A set of already approved markers (not necessarily for ovarian cancer) running on a (GMP) platform satisfies the claim and no IP rights are sought for the algorithm combining them.
- II. Same as I except that IP rights are sought for the algorithm combining them.
- III. The claim is satisfied by a combination of approved and unapproved markers. The unapproved markers are owned by one company planning to market the assay(s) as a standard ELISA that could be integrated in existing clinical platforms. The company may or may not have data to support claims as a recurrence marker or discriminator of a pelvic mass. IP rights may or may not be sought for the algorithm combining them.

## Levels of Complexity (cont.)

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- IV. The claim is satisfied by a combination of approved and unapproved markers. The unapproved markers are owned by one companies who plans to use the markers on a non-standard platform(s) such as mass spectrometry or Luminex. The company may or may not have data to support claims as a recurrence or discriminator of a pelvic mass. IP rights may or may not be sought for the algorithm to combine the markers.
- V. Same as IV except that the unapproved markers are owned by more than one company who plan to use different non-standard platforms. There are competing claims for the IP rights for the algorithm to combine them.

# Further thoughts about risk algorithms

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- Genetic tests such as BRCA1 and BRCA2 are used to define risk for breast or ovarian cancer in the setting of a family history. Genome Wide Association Studies may reveal patterns of single nucleotide polymorphisms (SNPs) that predict risk in women without a family history.
- Besides use of the serum or genetic markers to define risk, it also likely that certain demographic and medical factors might be included in risk algorithms.
- What would be the approval process for a SNP panel? To what extent would the FDA need to be involved in a risk model based on demographic or medical factors?

*Thanks for your attention*

Discussion