Evidence Utilization: Academic Health System Perspective

Robert C. Bast, Jr., M.D.
U.T. M.D. Anderson Cancer Center
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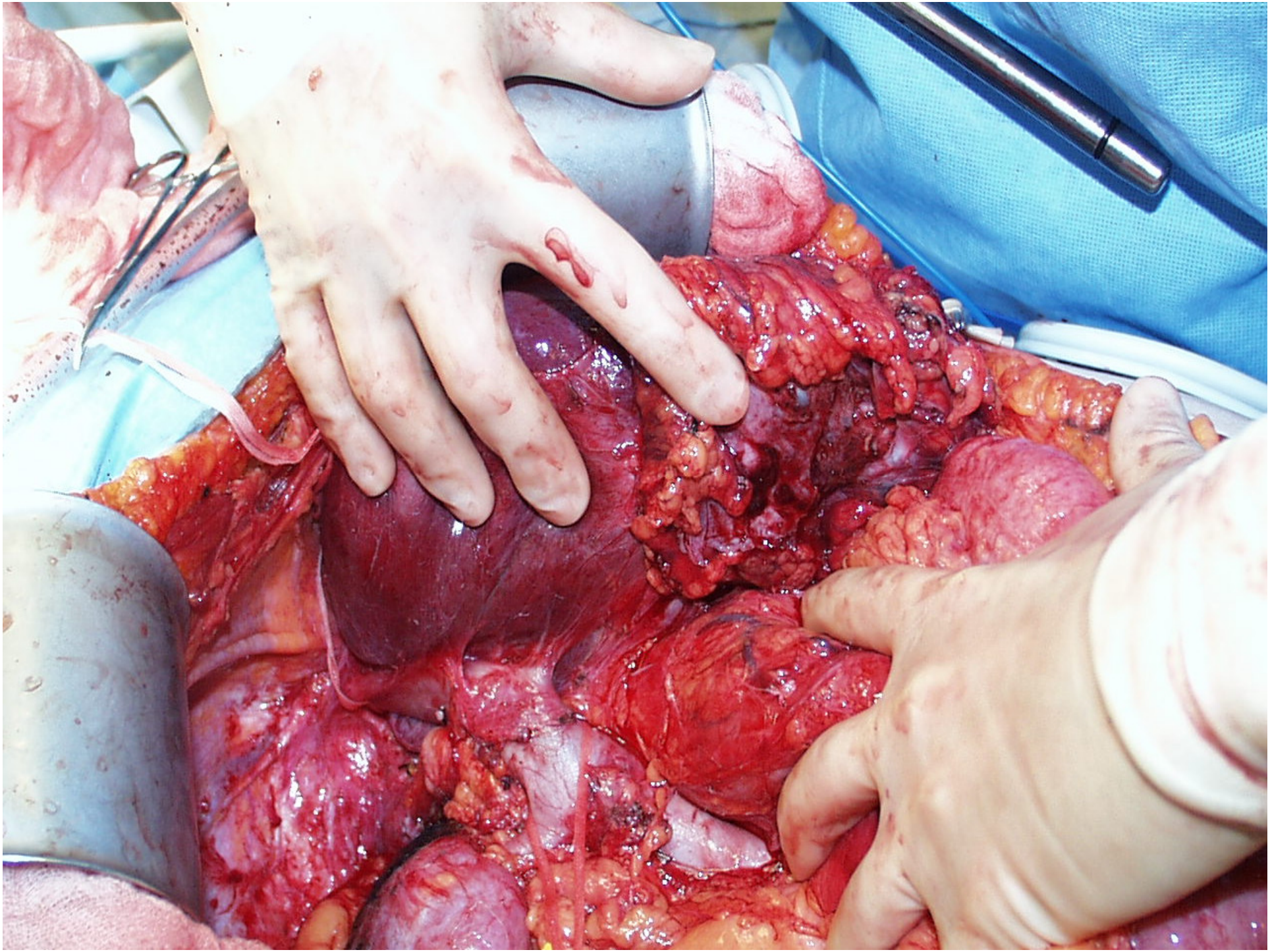
Conflicts: Dr. Bast receives royalties for CA125 and serves on Advisory Boards for Fujirebio Diagnostics and Vermillion.

Biomarkers to Personalize Care of Patients with Epithelial Ovarian Cancer

- Issues raised by Utilization of Biomarkers in a Particular Disease with Many Unmet Needs : Ovarian Cancer
- Neither Common nor Rare – 22,280 new cases and 15,500 deaths in 2012 despite Advances in Surgery and Chemotherapy
- Diagnosed late after spread throughout the Abdominal Cavity in Two-Thirds of Patients
- Often presents as a Pelvic Mass that can be Benign or Malignant

Biomarkers to Personalize Care of Patients with Epithelial Ovarian Cancer

- Referral to Appropriate Surgeons
- Early Detection
- Predicting Response to Primary Chemotherapy
- Predicting Response to Targeted Therapy



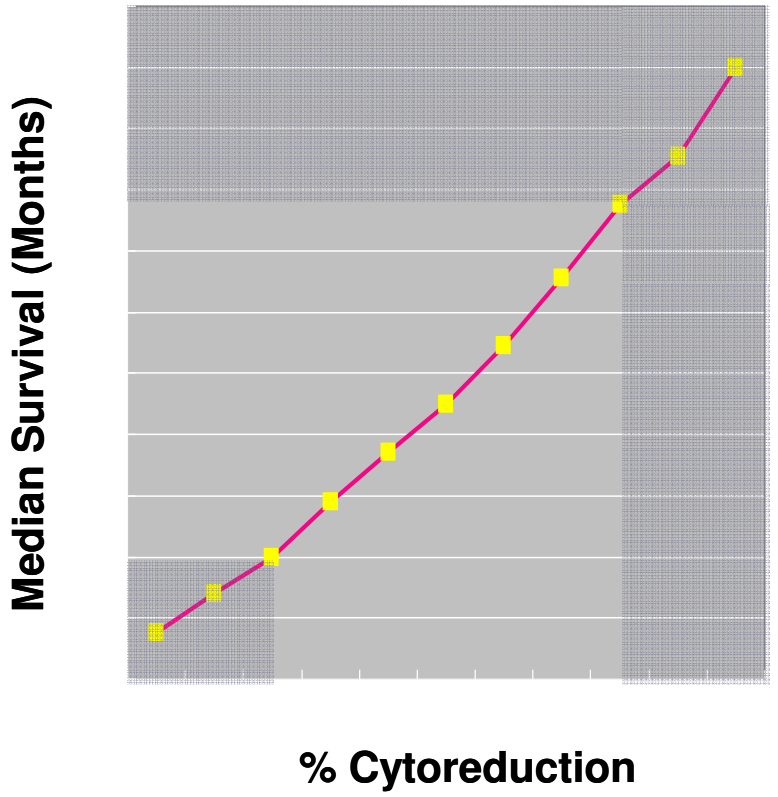
Primary Cytoreductive Surgery

- Primary Surgery Matters
- Even when all Ovarian Cancer cannot be removed, Prognosis is improved when Residual Metastases are decreased in size - <1 cm
- Not Clear whether this is Surgery or Biology – Prospective Randomized Trials are not Feasible in Previously Untreated Patients

Primary Cytoreductive Surgery

- Meta-analysis: 53 retrospective non-randomized studies (1989-98)
  - 81 cohorts (Stage III/IV)
  - N = 6885 patients

- Results
  - Optimal vs. not: 11 mos. (50% increase)
  - Each 10% ↑ in cytoreduction = 5.5% ↑ in survival



Bristow, J Clin Oncol 20:1248, 2002

Referral to Appropriate Surgeons

- Referral to a Gynecologic Oncologist improves Outcomes for Ovarian Cancer Patients
  - Higher Fraction of Optimal Cytoreduction
  - Higher adherence to Guidelines
  - Improved Overall Survival
- Only 30-50% of Women with Ovarian Cancer are Referred to Gynecologic Oncologists in the USA
  - Poor
  - Rural
  - Elderly - >70 years old
  - Decisions by General Gynecologists, Family Practitioners and Internists (Goff et al, Obstet Gynecol, 2011)

Referral to Appropriate Surgeons

- More than 200,000 Women Undergo Exploratory Surgery for a Pelvic Mass Each Year in the United States and 13-21% will Diagnose Cancer
- Biomarkers can distinguish Malignant from Benign Pelvic Masses
- In the UK a Risk of Malignancy Index (RMI) is used that incorporates CA125, Ultrasound and Menopausal Status, providing a Sensitivity of 71-88% at a Specificity of 74-97%

Jacobs et al, Br J Obstet & Gynaecol, 1990

- Biomarker Panels have been tested to improve on CA125 and not depend as critically on Ultrasound

ROMA Multicenter Validation Trial: "High Risk" Referred Participants

- **The ROMA algorithm using CA125, HE4 and Menopausal Status, but not TVS yielded:**
  - **93% Sensitivity and 75% Specificity Overall**
  - **76% Sensitivity and 75% Specificity Pre-Menopause**
  - **Negative Predictive Value is 93-94%**

Moore, et al, Gynecol Oncol, 2010

- **ROMA has been compared directly to the RMI and found Superior: 94% vs. 84% Sensitivity at 75% Specificity**

Moore, et al, Am J Obstet Gynecol, 2010

ROMA Multicenter Validation Trial: "Low Risk" Community Participants

- The ROMA algorithm was evaluated in a Second Trial with 472 Community Patients and 89 Cancers
  - 94% Sensitivity and 75% Specificity Overall
  - 100% Sensitivity and 75% Specificity Pre-Menopause
  - Negative Predictive Value was 99%

Moore, et al, Obstet Gynecol, 2011

- The ROMA was recently approved by the FDA

OVA1 Panel to Prompt Referral

- **Vermillion has also obtained FDA Approval for the OVA1 Panel of 5 Markers - CA125, Apolipoprotein A1, Transthyretin, Transferrin, and B2-Microglobulin - Measured by 5 Immunoassays**
  - **92% Sensitivity and 42% Specificity**
  - **85% Sensitivity and 45% Specificity Pre-Menopause**

Ueland et al, Obstet Gynecol, 2011

OVA1 vs. ROMA

- OVA1 has not been compared Directly to ROMA, but is likely to be as Sensitive, but substantially less Specific (75% vs. 40% or less)
- Both have High Negative Predictive Values (96%-99%)
- While the Difference in Specificity should not affect Patient Outcomes, it could affect distribution of Medical Resources
- Neither is a Screening test and should be used only for Women who are definitely going to Exploratory Surgery
- The Real Challenge is to encourage Use of Either Test

Evidence for Approval

- Consensus was obtained from a Retrospective Meta-analysis of non-randomized studies that Outcomes are improved by Referral of Ovarian Cancer Patients to Specially-trained Gynecologic Oncologists for Cytoreductive Surgery
- Randomized Prospective Trials were performed validating the Sensitivity and Specificity of Biomarkers and Algorithms for Identifying Women with Malignant Pelvic Masses that Require Treatment by a Gynecologic Oncologist
- Retrospective Assessment of Utility and Prospective Randomized Assessment of Validity

Biomarkers to Personalize Care of Patients with Epithelial Ovarian Cancer

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Rationale for Ovarian Cancer Screening

- **Ovarian Cancer Limited to the Ovaries (Stage I) can be Cured in up to 90% of Patients with Currently Available Therapy**
- **Disease that has Spread from the Pelvis (Stage III-IV) can be Cured in only 20% or Less**
- **Only 25% of Ovarian Cancers are Currently Diagnosed in Stage I**
- **Detection of Preclinical Disease at an Earlier Stage Could Improve Survival by 10-30%**

Epidemiological Requirements for Screening

- **Postmenopausal Prevalence: 1:2,500**
- **High Sensitivity: ≥ 75%**
- **Very High Specificity: 99.6%**
- **Positive Predictive Value: 10%**

Screening in the Prostate, Lung, Colon and Ovary (PLCO) Trial

- In the PLCO Trial, 37,500 Postmenopausal Women at Conventional Risk were followed with CA125 and Transvaginal Sonography (TVS) at Annual Intervals with Follow-up by Private Gynecologists
- No Stage Shift or Survival Advantage was observed
- In the PLCO Trial, CA125 alone had a PPV of 3.7%, TVS had a PPV of 1%, both together had a PPV of 23.5%, but 60% of Invasive Cancers would not be detected
- Specificity might be Improved by Combining CA 125 with Ultrasound Sequentially

Two Stage Strategies for Screening

- Used alone, Neither CA125 nor TVS has Adequate Specificity
- Ovarian Cancer is Associated with rising CA125 and Benign Disease is not
- Very High Specificity and Sensitivity can be attained when rising CA125 is used to trigger TVS in a Two Stage Strategy
- The Risk of Ovarian Cancer (ROC) Algorithm uses each Woman's own Baseline to determine whether there has been a significant increase

UKCTOCS Randomized Trial

- Two Hundred Thousand Postmenopausal Women at Average Risk have been Randomized to Three Groups
  - Control (101,359)
  - Annual TVS (50,639)
  - Annual CA125 with ROC Algorithm Prompting TVS (50,640)
- Completed Accrual
- Powered to test Survival
- Followed at least 7 Years
- Concludes 2015

The UKCTOCS Prevalence Screen

- **48% of cancers found by screening were in Stage I-II, doubling the detection of early stage disease**
- **CA125 followed by transvaginal ultrasound detected 89% of the ovarian cancers**
- **CA125 followed by ultrasound prompted 2.8 operations per case (O/C) compared to 36.2 O/C with annual ultrasound alone**
- **Ovarian cancers appeared to develop 2 years before they were detected by conventional means suggesting that annual screening will be effective**

Menon, Lancet Oncology, 2009

MDACC Ovarian SPORE Screening Trial

- **Smaller Trial of the CA125-TVS Arm in Postmenopausal Women at Average Risk for Developing Ovarian Cancer**
  - **Powered to test the Specificity and Positive Predictive Value of the Screen**
  - **Feasibility of Screening in Our Country**
  - **Develop a Serum, Plasma and Urine Bank over Multiple Years**

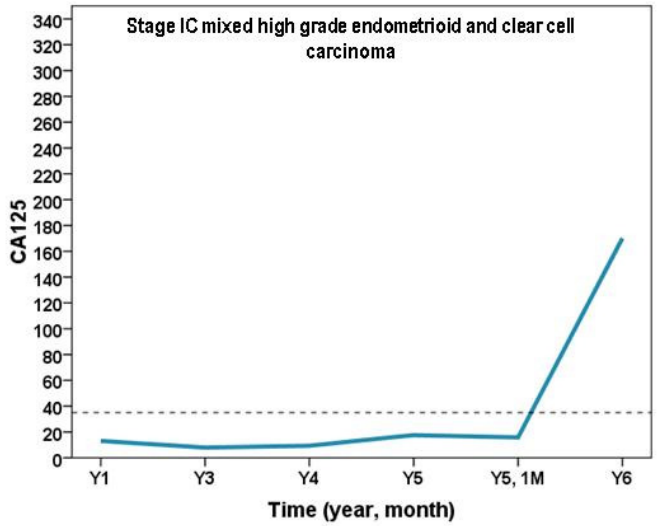
- **Collaboration with 7 Different Sites**
  - **U.T. M.D. Anderson Cancer Center, Houston, TX**
  - **Women's Hospital Clinical Research Center, Houston TX**
  - **John Stoddard Center, Des Moines, IA**
  - **Women and Infants Hospital, Providence, RI**
  - **Baylor University Medical Center, Dallas, TX**
  - **U.T. Southwestern Medical School, Dallas, TX**
  - **Atlantic Health, Morristown, NJ**

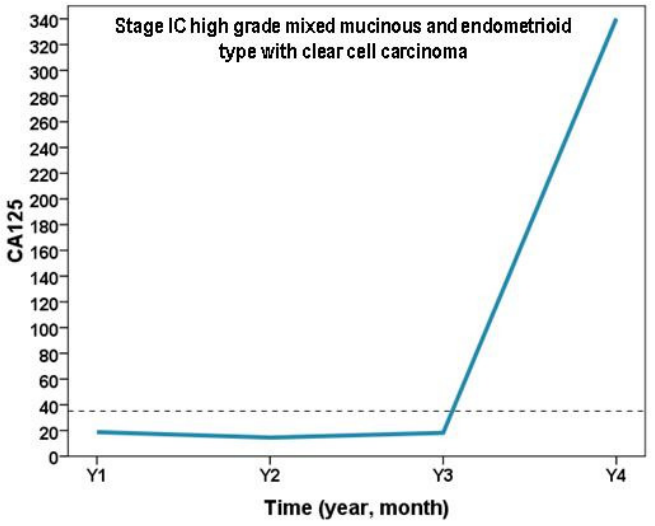
Lu, ASCO, 2010

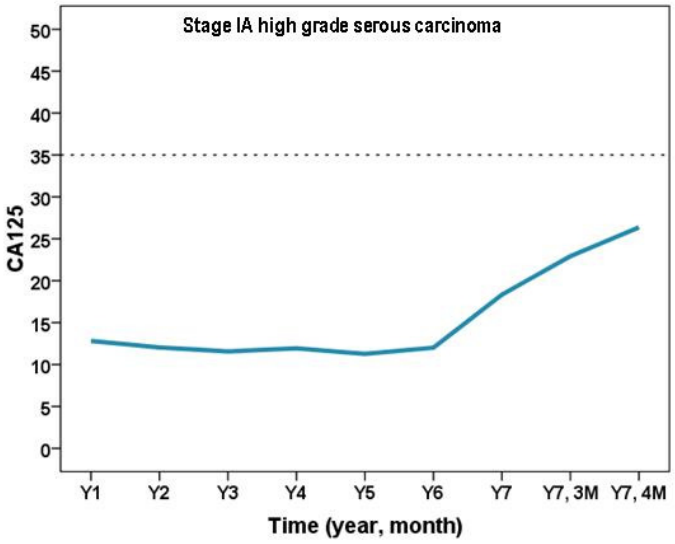
MDACC Ovarian SPORE Screening Trial

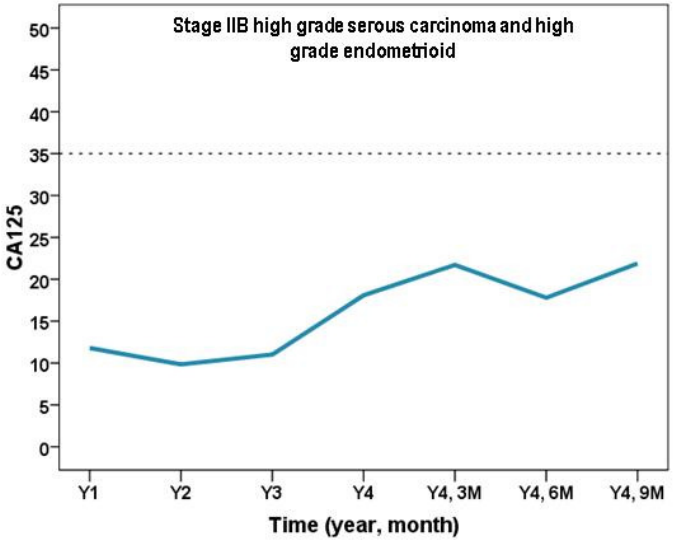
- **Over the last 10 years, 15,505 Samples have been obtained from 4,070 Postmenopausal Women at Conventional Risk**
- **Less than 0.9% have been referred for Ultrasound after each Annual Screening and 2.6% over multiple years on study**
- **Ten Operations have been prompted by the Algorithm and have detected 6 cases of ovarian cancer – two Borderline IA and four invasive high grade in Stages IA, IC, IC, and IIB**
- **With a Positive Predictive Value of 60% for all cancers and 40% for invasive cancers, no more than 3 operations will be required to detect each case of ovarian cancer using this strategy**

Lu, ASCO 2010


Stage IC mixed high grade endometrioid and clear cell carcinoma
CA125
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
Y1
Y3
Y4
Y5
Y5, 1M
Y6
Time (year, month)


Stage IC high grade mixed mucinous and endometrioid type with clear cell carcinoma
CA125
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
Y1
Y2
Y3
Y4
Time (year, month)


Stage IA high grade serous carcinoma
CA125
50
45
40
35
30
25
20
15
10
5
0
Y1
Y2
Y3
Y4
Y5
Y6
Y7
Y7, 3M
Y7, 4M
Time (year, month)


Stage IIB high grade serous carcinoma and high grade endometrioid
CA125
50
45
40
35
30
25
20
15
10
5
0
Y1
Y2
Y3
Y4
Y4, 3M
Y4, 6M
Y4, 9M
Time (year, month)

Evidence for Approval

- **Prospective Randomized Survival Study in the United Kingdom**
- **Prospective Single Arm Study of Specificity and Positive Predictive Value in the United States with Consistent Outcomes**
- **Are Multinational Trials Acceptable?**
- **Assuming survival is improved, is this Evidence adequate?**

OvaCheck™

- **Proteomic spectra were generated by surface-enhanced laser desorption and ionization (SELDI) mass spectroscopy**
- **A training set of spectra were derived from analysis of serum from 50 healthy women and 50 patients with ovarian cancer using an iterative searching algorithm.**
- **A pattern that distinguished ovarian cancer sera was used to classify serum samples from 66 healthy women and 50 women with ovarian cancer including 18 with stage I disease.**
- **All cancers were correctly classified (93-100%), as were 95% of 66 healthy individuals (87-99%).**

Petricoin et al, Lancet, 2002

OvaCheck™

- Encouraging preliminary study
- Few early stage patients
- Evidence of Experimental Bias Associated with Experimental Design

  Baggerly et al, Bioinformatics, 2004
  Baggerly et al, Cancer Inform, 2005

- In 2004 the FDA cautioned Correlogic against Sale as a Laboratory Developed Test and Ovacheck was Withdrawn
- Over the years, the Algorithm and Goals have changed

OvaSure™

- Multiplex Panel of Six Biomarkers reported by Visintin et al, Clin Cancer Res, 2008.
  - Leptin
  - Prolactin
  - Osteopontin
  - IGF II
  - M-CSF
  - CA125
- Marketed by LabCorp as a Laboratory Developed Test or "Bench Assay"
  - CLIA assures that the Proteins are well Assayed
  - Does Not assure that the Assay Actually detects Early Stage Ovarian Cancer
  - Does Not Assure that there is an Acceptable Level of "False Positive" Values

OvaSure™

- One Published Study with the 6 Biomarkers
- Sensitivity of 95.3%
  - Includes not just Stage I, but Stage I-IV
  - Marker Levels are Higher in Advanced Stage
  - 13 Stage I Cases
  - Sensitivity for Early Stage Disease not Clear
- Specificity 99.4%
  - 20 Operations Per Case of Ovarian Cancer Detected, unless combined with Transvaginal Sonography
  - No "High Risk" Controls, although this is the Population Targeted According to the LabCorp Website
  - CA125 has Lower Specificity in Premenopausal women at "High Risk" for Ovarian Cancer

OvaSure™

- Instead of using Distinct “Training” and “Validation” sets, The Yale group identified the Best 6 Markers and developed a Mathematical Formula by using both the “Training” and “Validation” Groups to best “fit” the Validation Data.
- Dr. Marty McIntosh had calculated that If the Markers developed from the “Training” set alone were Applied to the Validation Group, the Actual Sensitivity (Stage I-IV) would be 84-88% and the Specificity 95%
- In August 2008, the FDA suggested that the assay was a “high risk test that had not received adequate clinical validation” and that had not been developed “in house” at LabCorp, but at Yale.
- LabCorp withdrew OvaSure™ from the Market in 2008.

The Downside of Marketing Inadequately Evaluated Screening Tests

- **As Only 1 Postmenopausal Woman in 2,500 will have Ovarian Cancer, any decrease in Specificity will Result in Large Numbers of "False-Positive" Tests in Women who do not have Ovarian Cancer**
  - **Large Numbers of Healthy Women will be Alarmed Unnecessarily**
  - **Expensive Imaging Studies will be Ordered**
  - **Many Unnecessary Operations will be Performed**
- **Unless a Screening Test Detects the Earliest Stages of Ovarian Cancer in a Significant Fraction of Women, No Benefit will be Received for the Anxiety, Inconvenience and Expense of the Blood and Imaging Tests, as well as the Pain and Risk of Surgery**

Evidence for Approval

- Clear FDA Guidance is needed for Laboratory Developed Tests
- Some Diagnostics Companies have behaved Responsibly – Human Genome Science – Oncotype Dx™
- Where Significant Risk is involved, should LDTs be held to the Same Standard as IDEs/PMAs?

CA125: Timeline

1979	Development of the OC 125 Antibody
1981	Publication of OC 125 in the *Journal of Clinical Investigation*
1983	Publication of CA 125 Assay in the *New England Journal of Medicine*
1987	Approval of CA 125 by the FDA for Detection of Disease at Second Look Laparotomy
1986 - 1988	Stockholm Screening Study of 5,550 Women - Nina Einhorn
1986 - 1990	United Kingdom Screening Study of 22,000 Women (Barts II) - Ian Jacobs
1995	Skates Algorithm Developed
2001	UKCTOCS Survival Study Initiated
2015	Anticipated Completion of Follow Up for UKCTOCS

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Predicting Response to Primary Therapy

- Most Ovarian Cancer Patients are treated routinely with Carboplatin and Paclitaxel
- From GOG 132, we know that only 70% of patients respond to Platinum-based Therapy and only 42% respond to Paclitaxel as a Single Agent
- No synergy exists between Carboplatin and Paclitaxel
- More than half of Patients waste the Opportunity to Receive Other Agents during Primary Therapy
- To date there are no markers or marker panels that predict sensitivity or resistance to paclitaxel and platinum with sufficient accuracy to be clinically useful
- Biomarkers with High Negative Predictive Value are needed

Evidence for Approval

- Is Accurate Prediction of Failure to respond to a Toxic Drug adequate evidence of Utility?
- Is 90% Negative Predictive Value an Adequate Benchmark?
- Are Prospective Trials Required to Validate Biomarkers or Panels of Biomarkers?

Biomarkers to Personalize Care of Patients with Epithelial Ovarian Cancer

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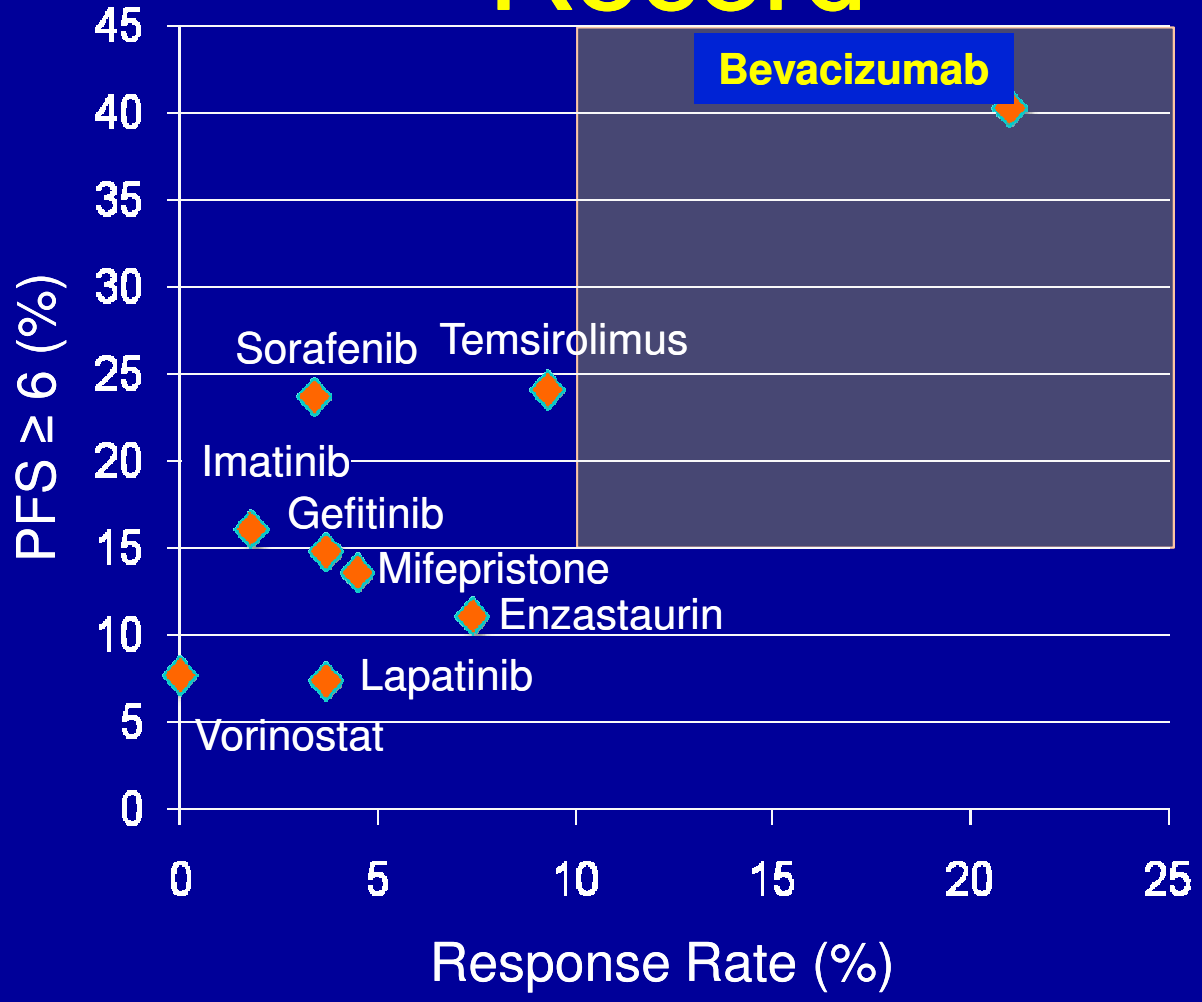
GOG 170 Series: Track Record



Biomarkers for Response to Bevacizumab

- Important Unmet Need
- Several Potential Candidates
  - Circulating Endothelial Precursors
  - Perfusion on DC MRI
  - Angiogenic Signatures on Gene Expression and Protein Arrays
- Given the Potential Toxicity and Cost, a test with High Negative Predictive Value would be Useful
- Is there a Place for a Test with Positive Predictive Value?

Evidence for Approval

- Is Accurate Prediction of Failure to respond to a Toxic and Expensive Drug Adequate evidence of Utility?
- Is 90% Negative Predictive Value an Adequate Benchmark?
- What is a reasonable level for Positive Predictive Value – Statistical Significance or Clinical Utility?
- What sort of Prospective Trials would be required?