Stage Shift in Ovarian Cancer Early Detection Trials in High-Risk Women

EDRN Steering Committee Meeting
27-28 October 2020

Steven J. Skates
Massachusetts General Hospital and Harvard Medical School

Disclosures

GRAIL
Guardant
Abcodia
Mercy BioAnalytics
LUNGevity

Off label use of CA125

Benefit to Harms Scale

1. HCC – how many MRIs to detect one liver cancer?
2. Gastric – how many EGDs with biopsy to detect one gastric cancer?
3. Pancreatic – CT -> endoscopic ultrasound and biopsy - # per pancreatic cancer detected
4. Breast – existing screening modality – but 12-33 positive on mammography per cancer, and 5-6 biopsies per breast cancer detected by mammography. Same goal for blood test?
5. Lung Cancer – LDCT -> Bx via thoracotomy - # thoracotomies/cancer
6. Ovarian – # surgeries per OVCA detected

Stage Shift

Basis of Early Detection: Disease is more curable in early stages

- Breast, colon, lung, cervical cancer
- Ovarian, kidney, liver cancer
- Brain cancer, pancreatic cancer

Stage Shift as surrogate endpoint

Analogous to PFS instead of OS in therapeutic trials
- Earlier endpoint – shorter trial, fewer patients
- PFS is predictive of OS

Stage Shift

Potential Definitions

Increase in proportion of cases detected in early stage disease
- Overdiagnosis: PSA and prostate cancer

Decrease in proportion of cases detected in late stage disease
- Inverse of proportion in early stage – overdiagnosis

Decrease in absolute incidence of late stage disease
- Reduces number of cases in late stage
- Eventually leads to reduction in mortality
- Reduces sample size
- Reduces duration

- Claim: this endpoint increases sample size compared to proportion

Ovarian Cancer Early Detection Trials in the High-Risk Population

1. CGN/EDRN/SPORE/GOG-0199 screening trials
2. UKFOCSS – UK Familial Ovarian Cancer Screening Study

Early Stage in BRCA1 women – 10% JAMA 2000

Pilot Screening Trial of High-Risk Women

CGN, Ovarian SPOREs, EDRN Collaboration

Prospective US multi-center single arm screening trial

Aim: Determine stage shift compared to historical controls

2,400 high risk women followed every 3 months with ROCA

High Risk:

- Proband BRCA positive, or 1st or 2nd degree relative
- Two or more breast or ovarian cancers in self, or 1st or 2nd degree relatives (same lineage)
- Ashkenazi Jewish descent and one close relative with breast or ovarian cancer

Ovarian Cancer Screening Trial in High Risk Women

PI: Steven Skates MGH
Co-PIs: Karen Lu: MD Anderson Cancer Center
Andy Berchuck : Duke University Medical Center

Site PIs:

John Schorge: UTSW Dallas
Claudine Isaacs: Georgetown
Saundra Buys: HCI, Utah
Wendy Brewster: UCI
Chuck Drescher: FHCRC
Powel Brown: Baylor
Susan Domchek: U Penn
Deborah Armstrong: Hopkins
Alex Miller: San Antonio
William Newland: Iowa
Mark Greene: NCI/GOG
Susan Davidson: Colorado
Ira Horowitz: Emory
Leslie Walton: UNC
Paula Ryan: MGH
Judy Garber: DFCI
Mack Barnes: UAB
Mary Daly: Fox Chase
Joseph Kelly: Magee
Patrice Watson: Creighton
Lee-May Chen: UCSF

Statistical Center: Dianne Finkelstein
Medical Informatics: Prakash Nadkarni

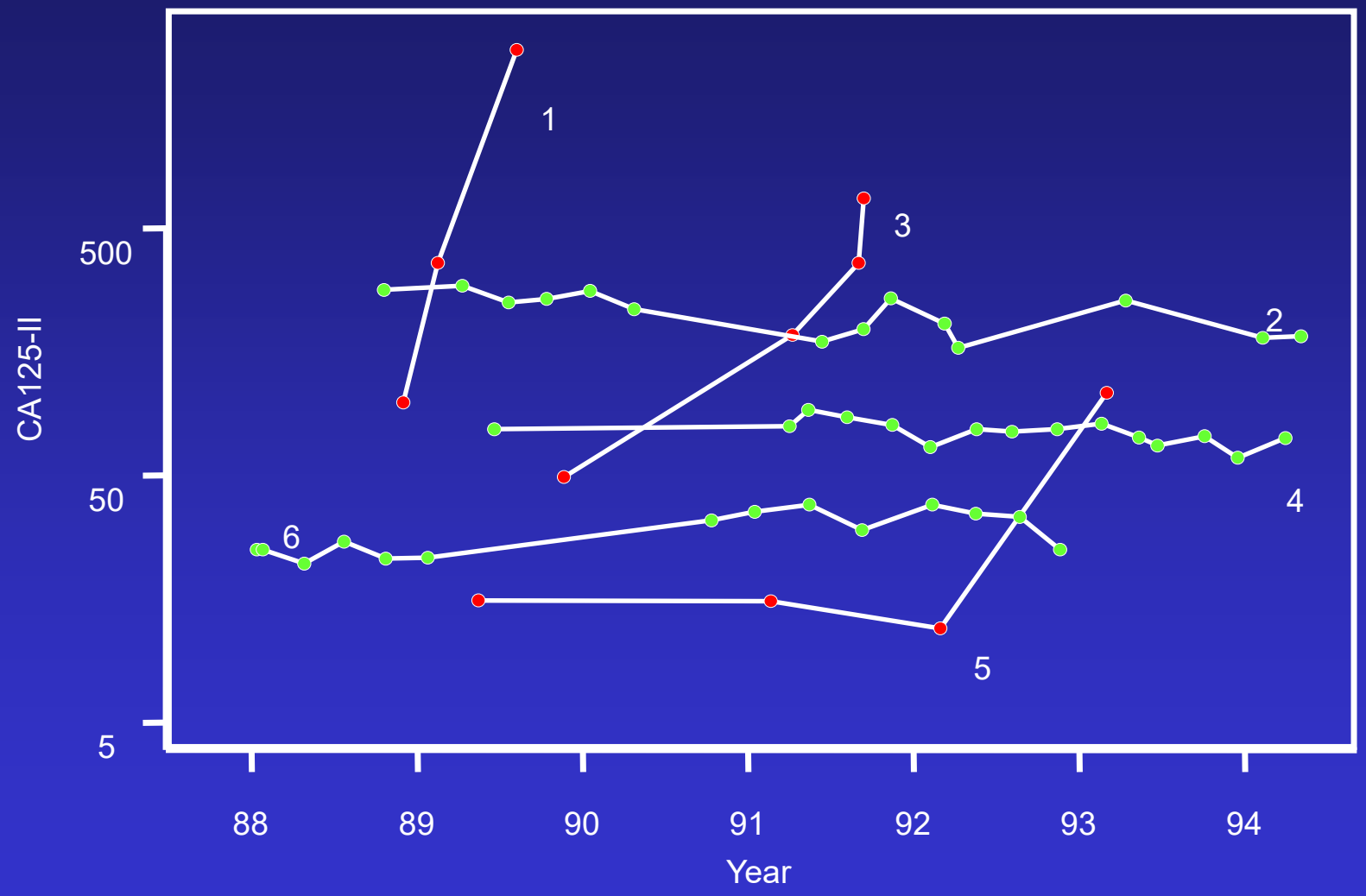
NCI: Carol Kasten-Sportes, Susan Nayfield

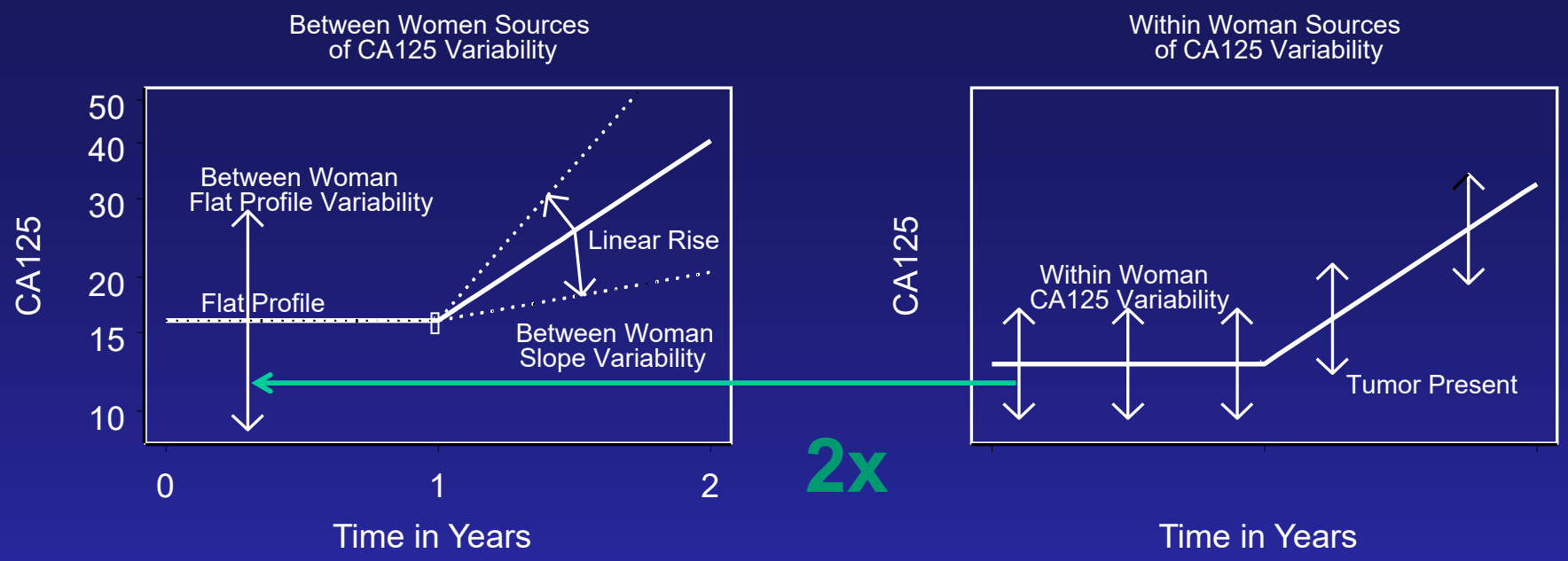
Funding: NCI

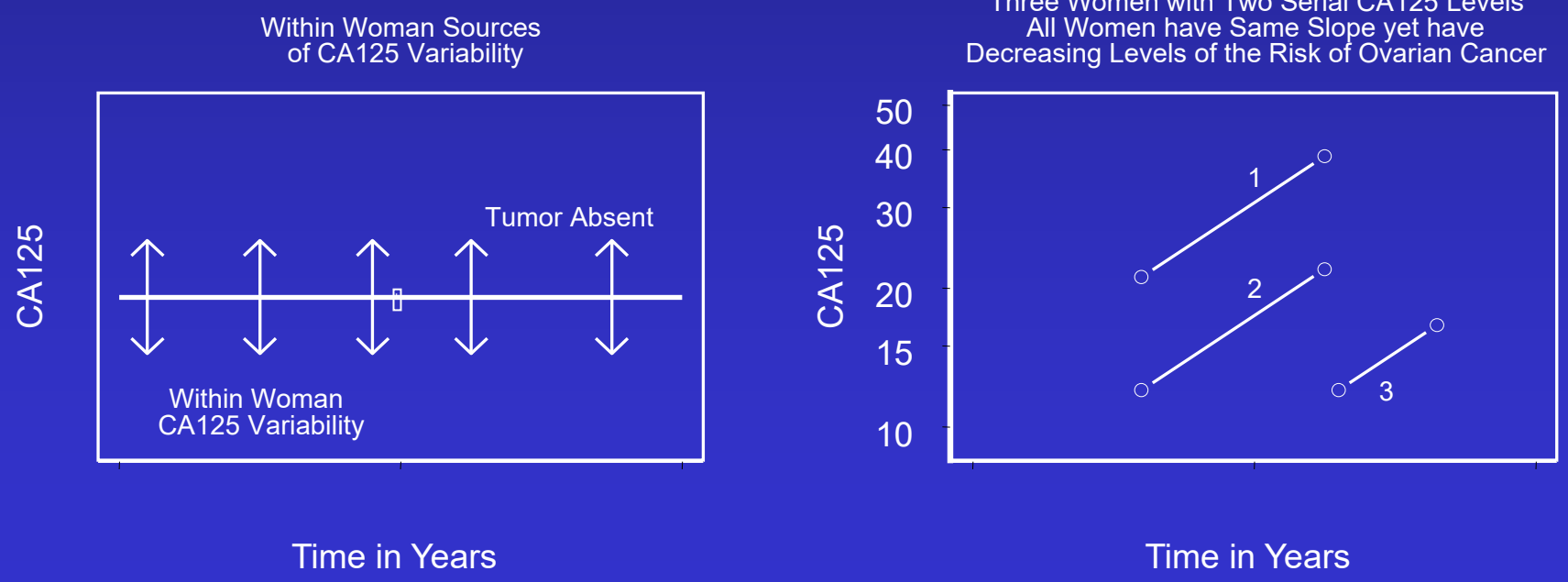
GOG-199 Study (PI: Mark Greene)

- Compare outcomes in high risk women choosing between
  - RRSO
  - Screening with longitudinal CA125
- 1,600 women enrolled in screening arm
- Five years of screening – every 3 months

CA125 in 3 women with occult ovarian cancer & 3 women without ovarian cancer

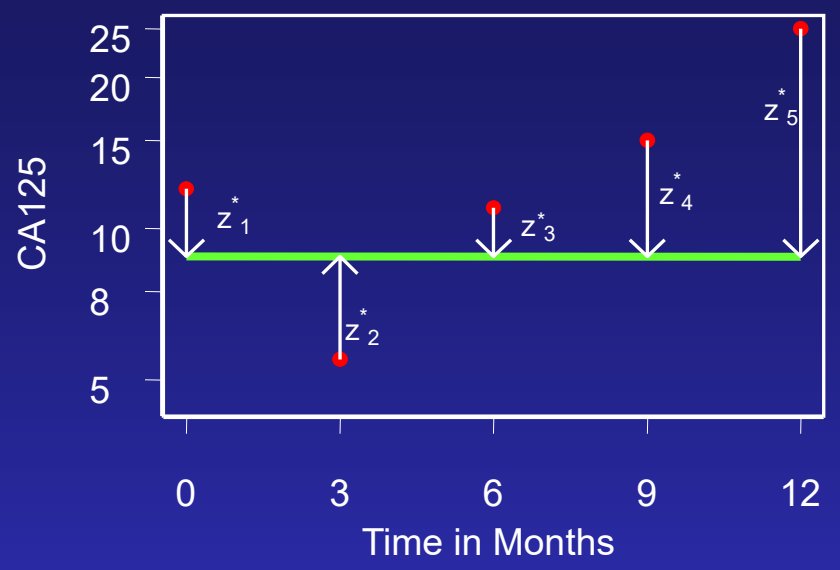


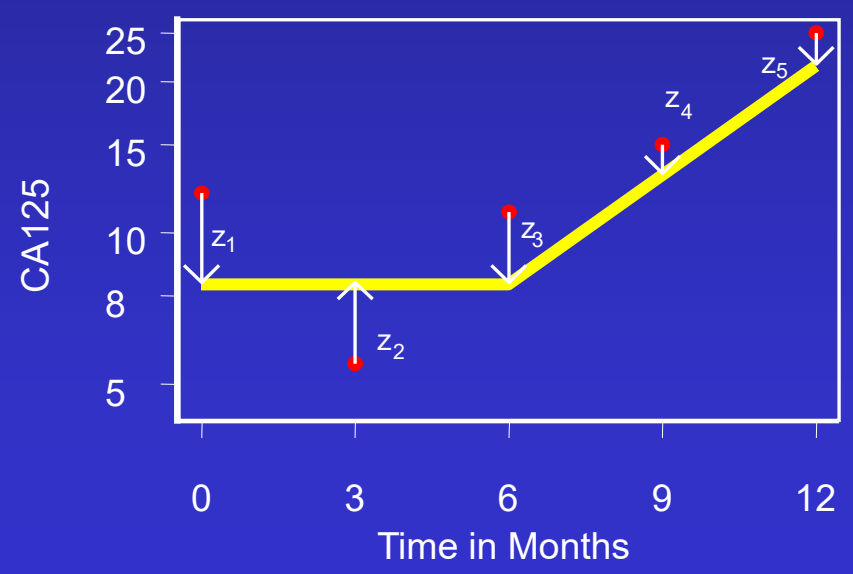




"Velocity" unreliable

Probabilistic Machine Learning





Red Dots: CA125 Values
Green Line: Flat Pattern
Yellow Line: Elbow Pattern

Initial odds: From woman's age

Z-values: Distance from Pattern to CA125 values. Smaller distance implies pattern is more likely.

Final Distance:
- Sum of squared Z values
- Divided by CA125 variability σ*

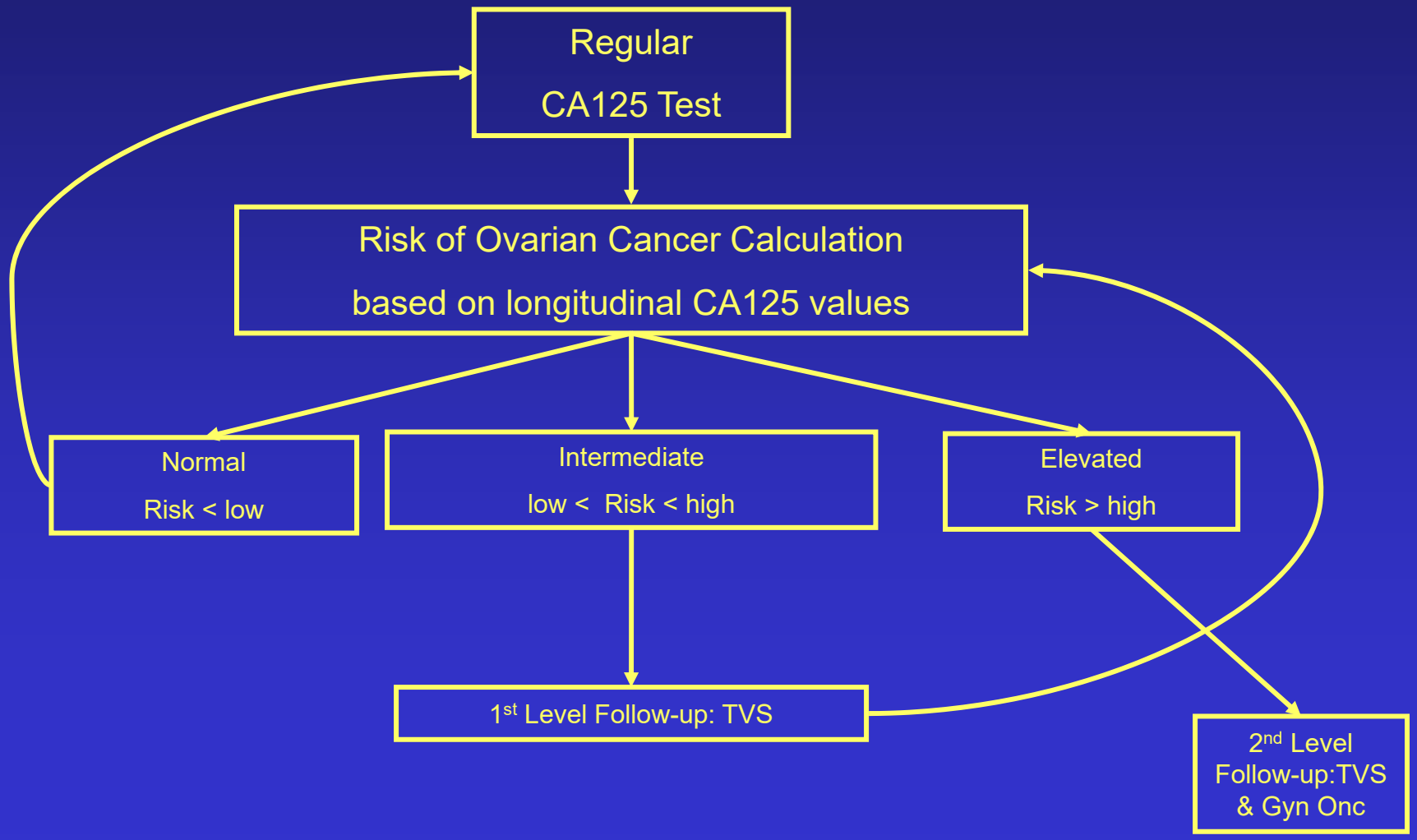
Odds: Ratio of average "yellow" to average "green" distance

Final odds: (Initial odds) * (odds ratio)

Probability: Odds/(Odds+1)

Integrate over multivariate posterior distribution using Markov chain Monte-Carlo draws

Longitudinal CA125 Design



CGN-EDRN-SPORE & GOG-199

13,080 screening-years >38,000 CA-125 tests

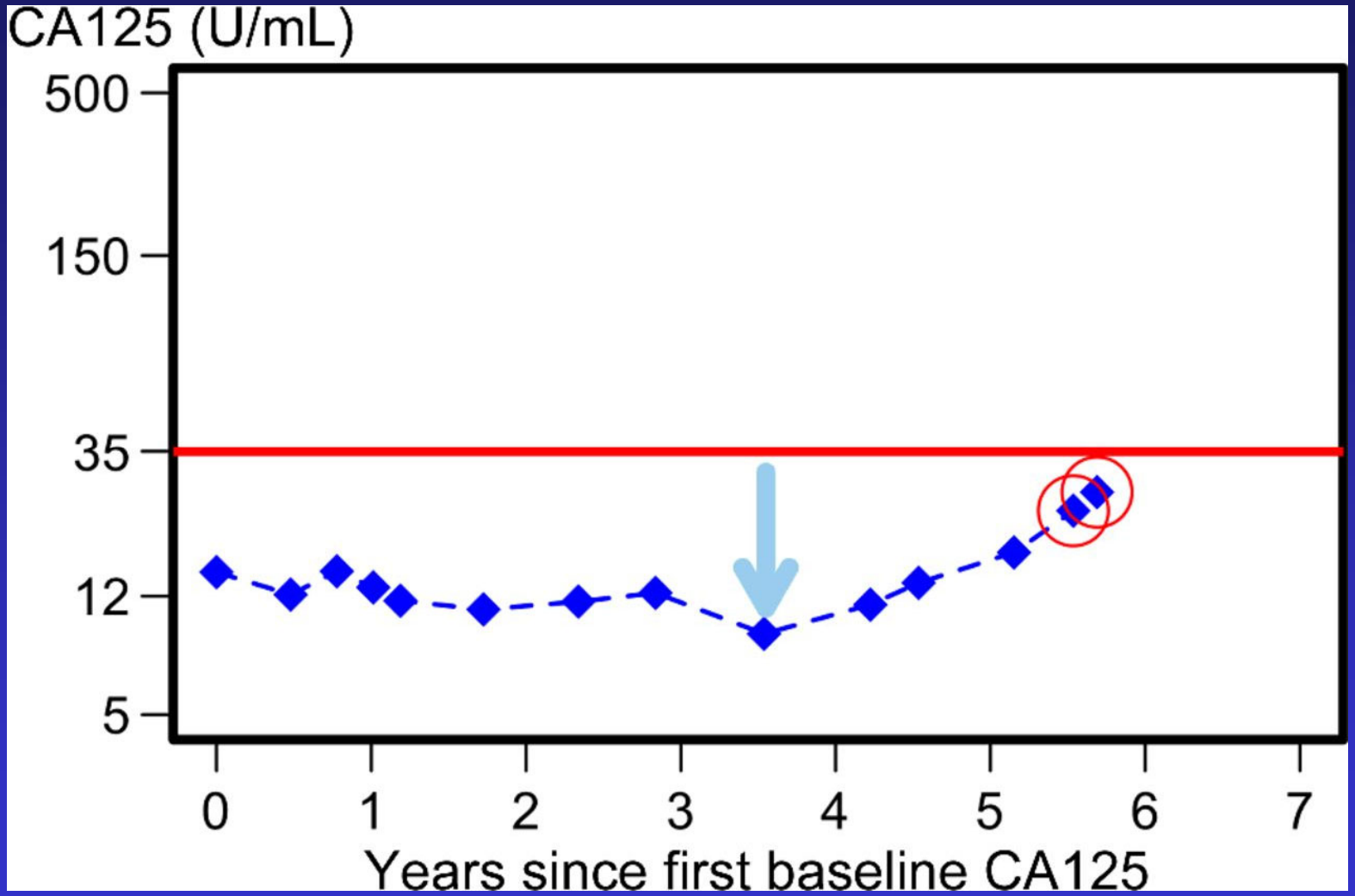
ROCA

- 2,269 eligible subjects
- 6,979 screening-years

GOG-199

- 1,458 eligible subjects
- 6,101 screening-years

Early detection of ovarian cancer via ROCA even though CA125 remains below 35 U/mL.



Steven J. Skates et al. Clin Cancer Res 2017;23:3628-3637

©2017 by American Association for Cancer Research

Clinical Cancer Research
AACR American Association for Cancer Research

Stage Shift

CGN-EDRN-SPORE-GOG (13,080 WSY 19 cases)

50% vs. 10% (historical control) $p = 0.016$ CCR 2017

UKFOCSS (13,728 WSY 19 cases)

53% vs. 6% (diagnosed > 1 yr after end of screening) $p < 0.001$ JCO 2017

3.3-fold greater incidence than normal risk (1 in 2,300/yr)

- Family history rather than BRCA carriers
- Lower risk spectrum

Stage Shift

High-Risk

- comparison to historical control or close contemporary
- 3-fold decrease in WSY

Normal Risk RCT – surrogate endpoint

- Late stage incidence reduction (if concern re overdiagnosis)
- Reduced sample size
- Shorter duration to surrogate endpoint
- Follow-up to mortality

Correlation between reduction in late stage and mortality reduction

Acknowledgements

Early Detection Research Network

Bob Knapp, Bob Bast, Karen Lu, Andy Berchuk
Ian Jacobs, Usha Menon, Max Parmar
Michael Birrer, Michael Gillette, Ronald Drapkin

Christos Patriotis, Sudhir Srivastava, Lynn Sorbara

Thank you!