UCL Elizabeth Garrett Anderson Institute for Women's Health

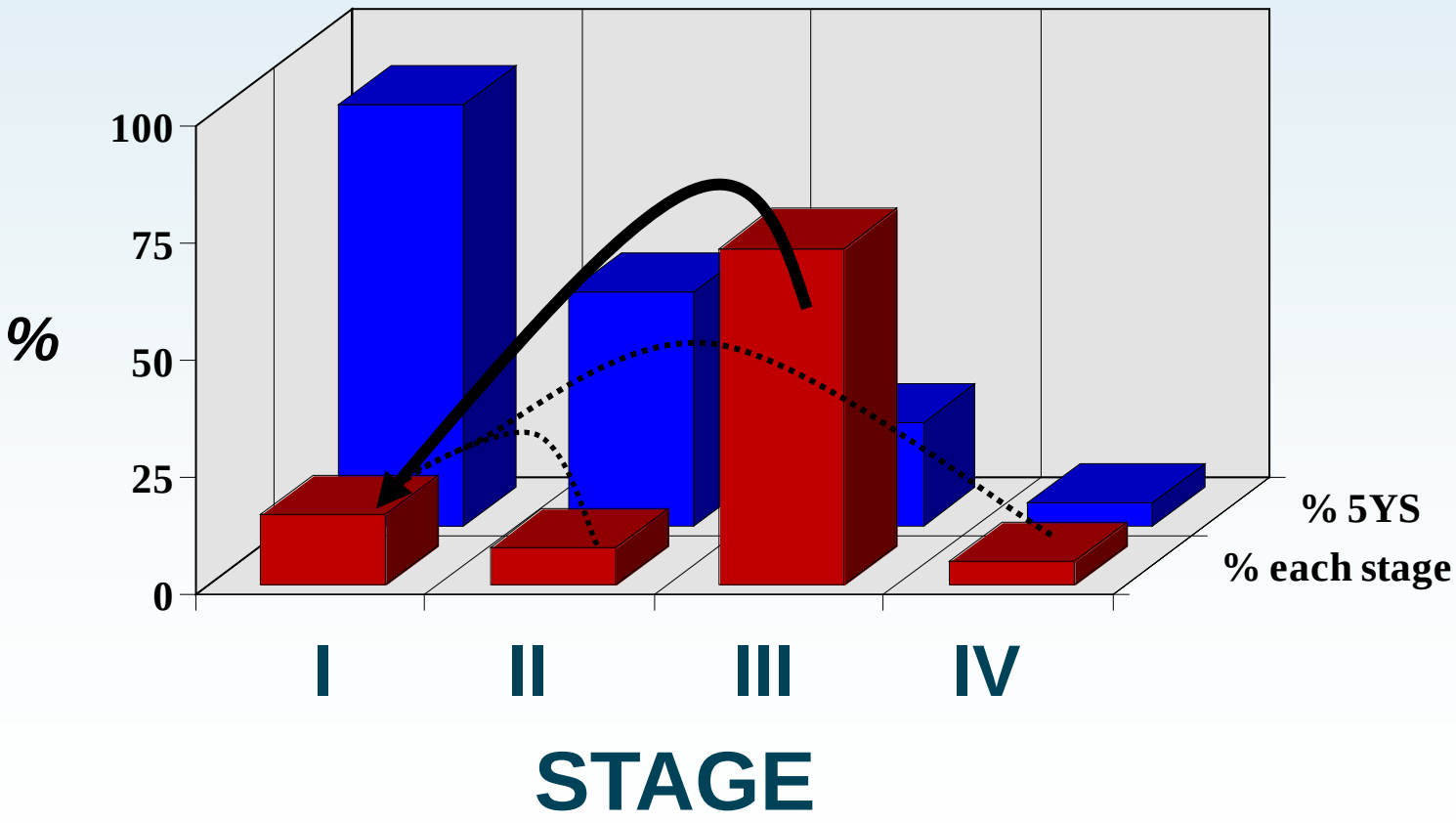
UCL

Ovarian Cancer Screening

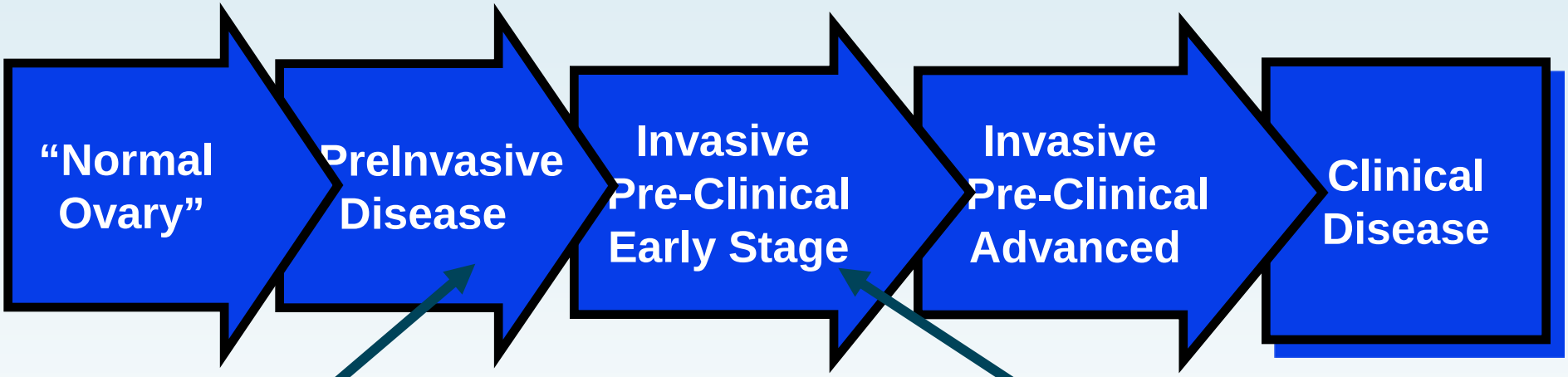
International Cancer Screening Network
Biennial Meeting, Oxford
June 2010

Ian Jacobs
On behalf of the UKCTOCS & UKFOCSS Teams
Institute for Women's Health, UCL

Rationale of Screening for Ovarian Cancer



Is the Natural History of Ovarian Cancer amenable to Screening ?



No known premalignant stage

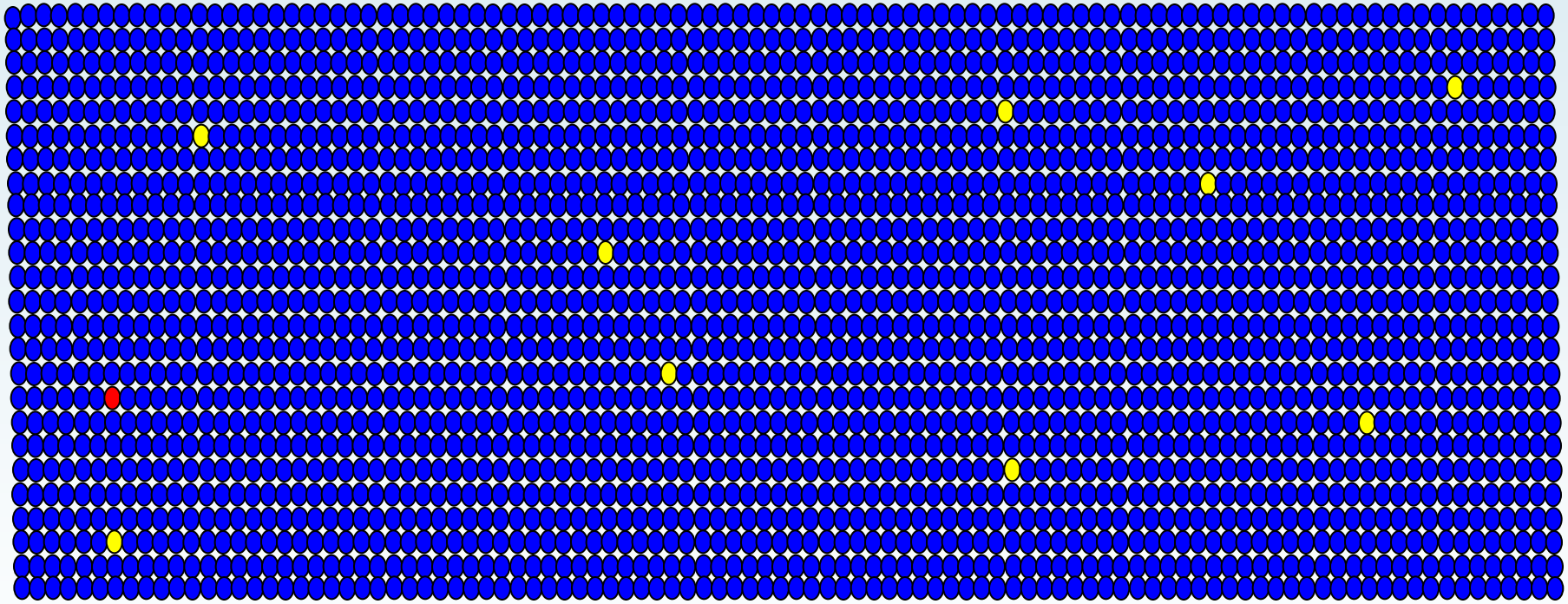
Duration uncertain

Does preclinical detection improve prognosis?

Lead time bias

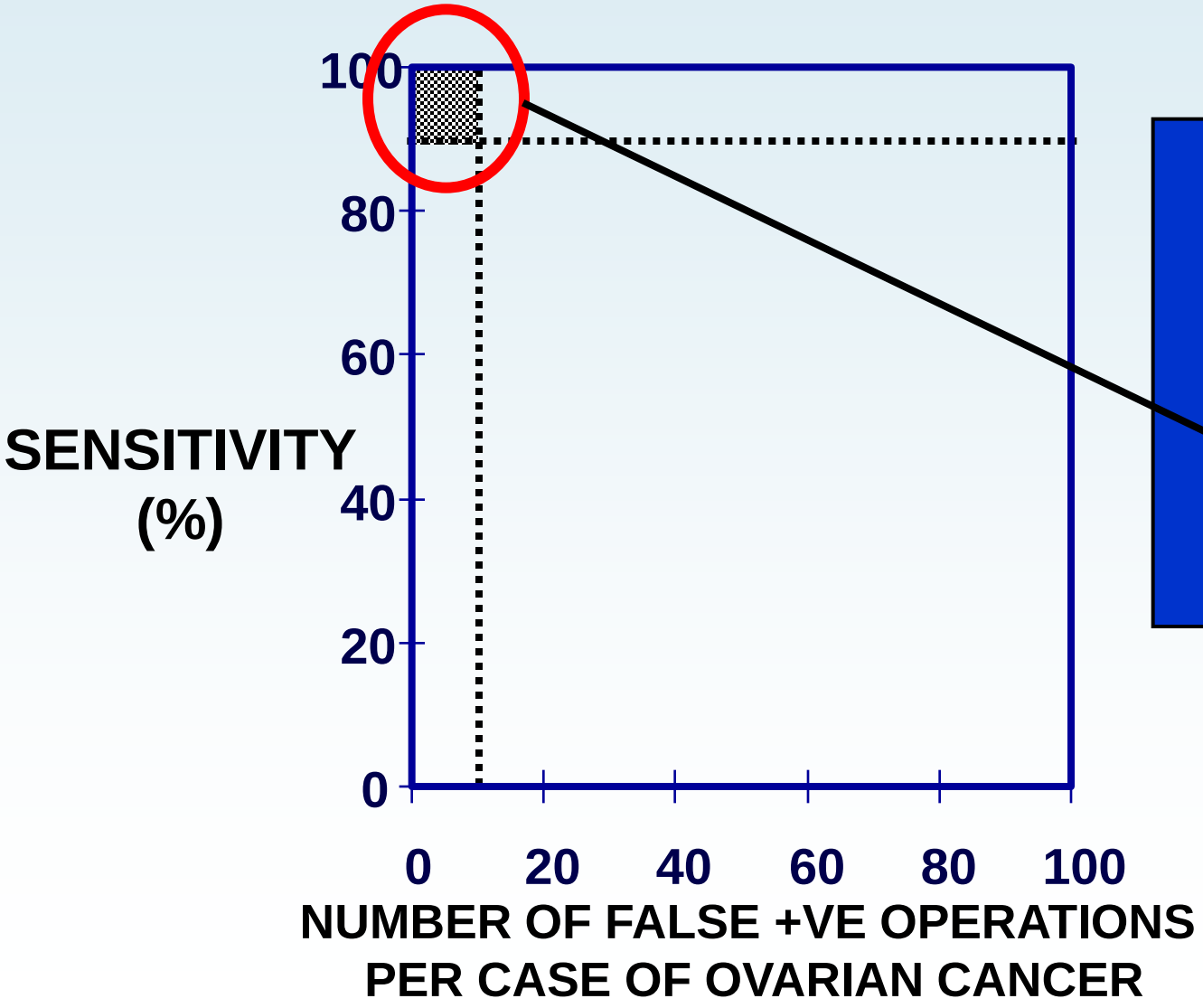
Length time bias

The Challenge of Ovarian Cancer Screening
Incidence 1 in 2,500 pa in women >50y



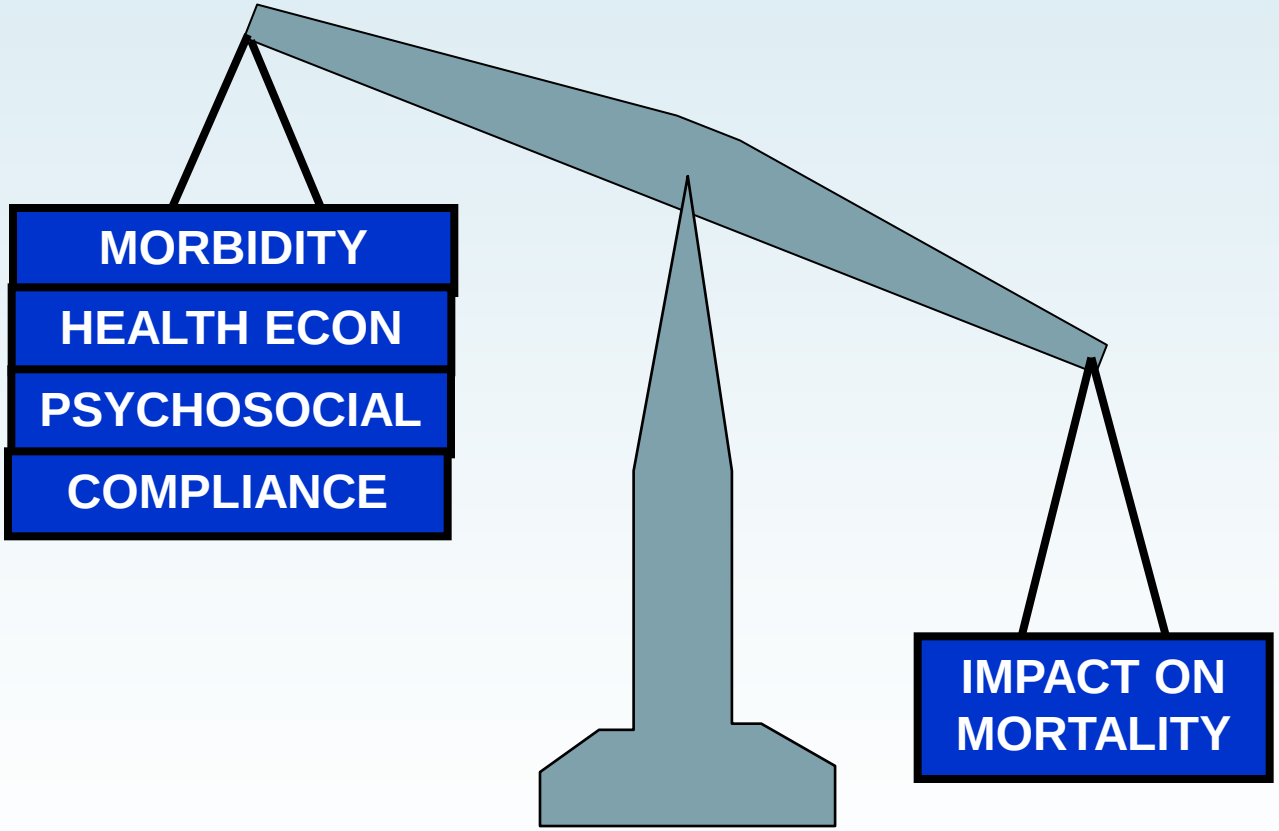
Achieving a 10% PPV requires 99.6% specificity on general population screening

Achieving adequate Sensitivity & Specificity

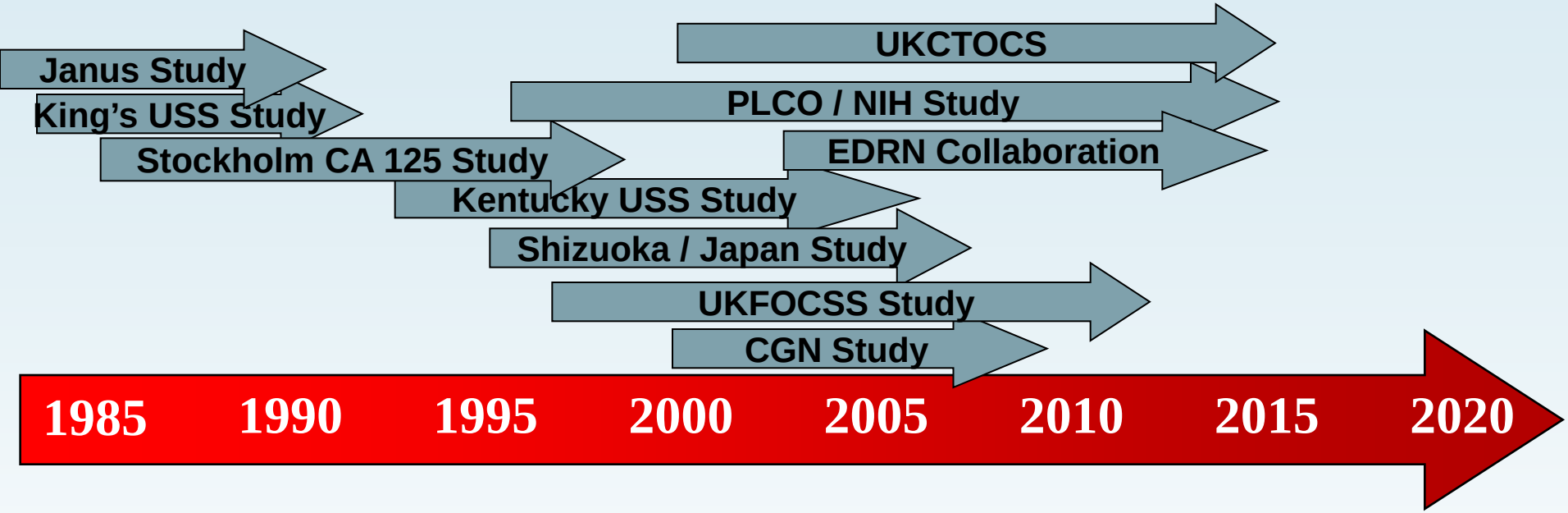


Target performance or an ovarian cancer screening strategy

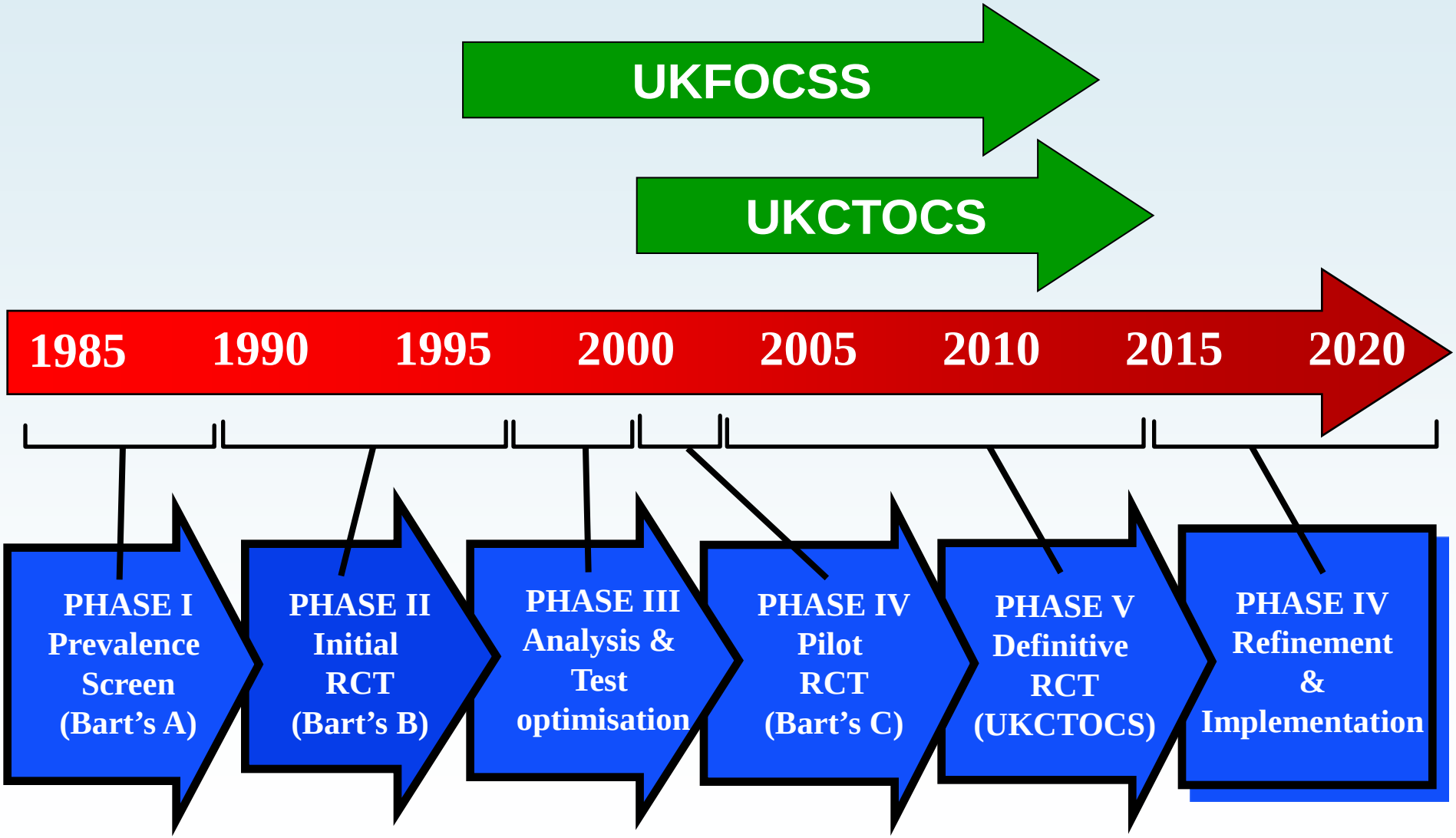
Will Screening Decrease Mortality? Answer 2013/14



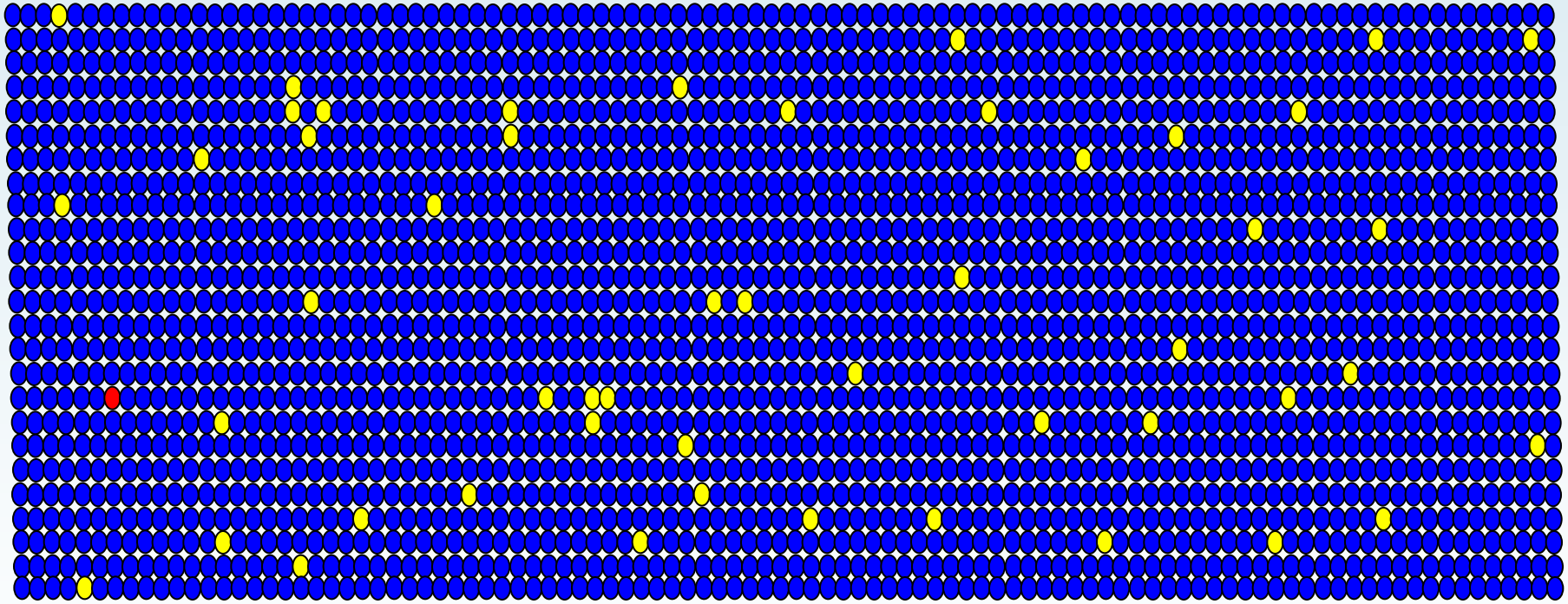
OVARIAN CANCER SCREENING



OVARIAN CANCER SCREENING

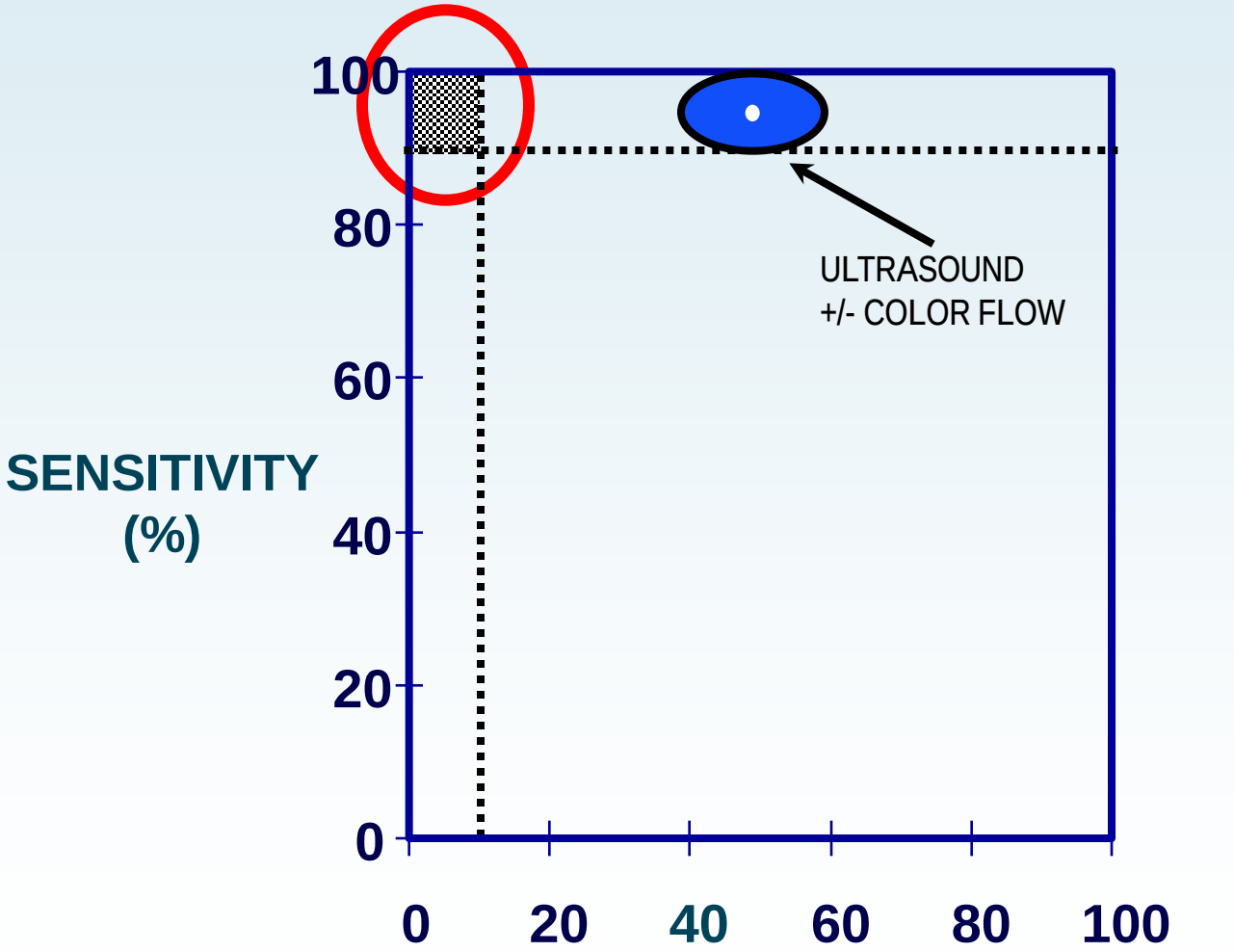


Initial Ultrasound Studies



King's College, 1980's:
50 unnecessary operations for each patient detected with ovarian cancer

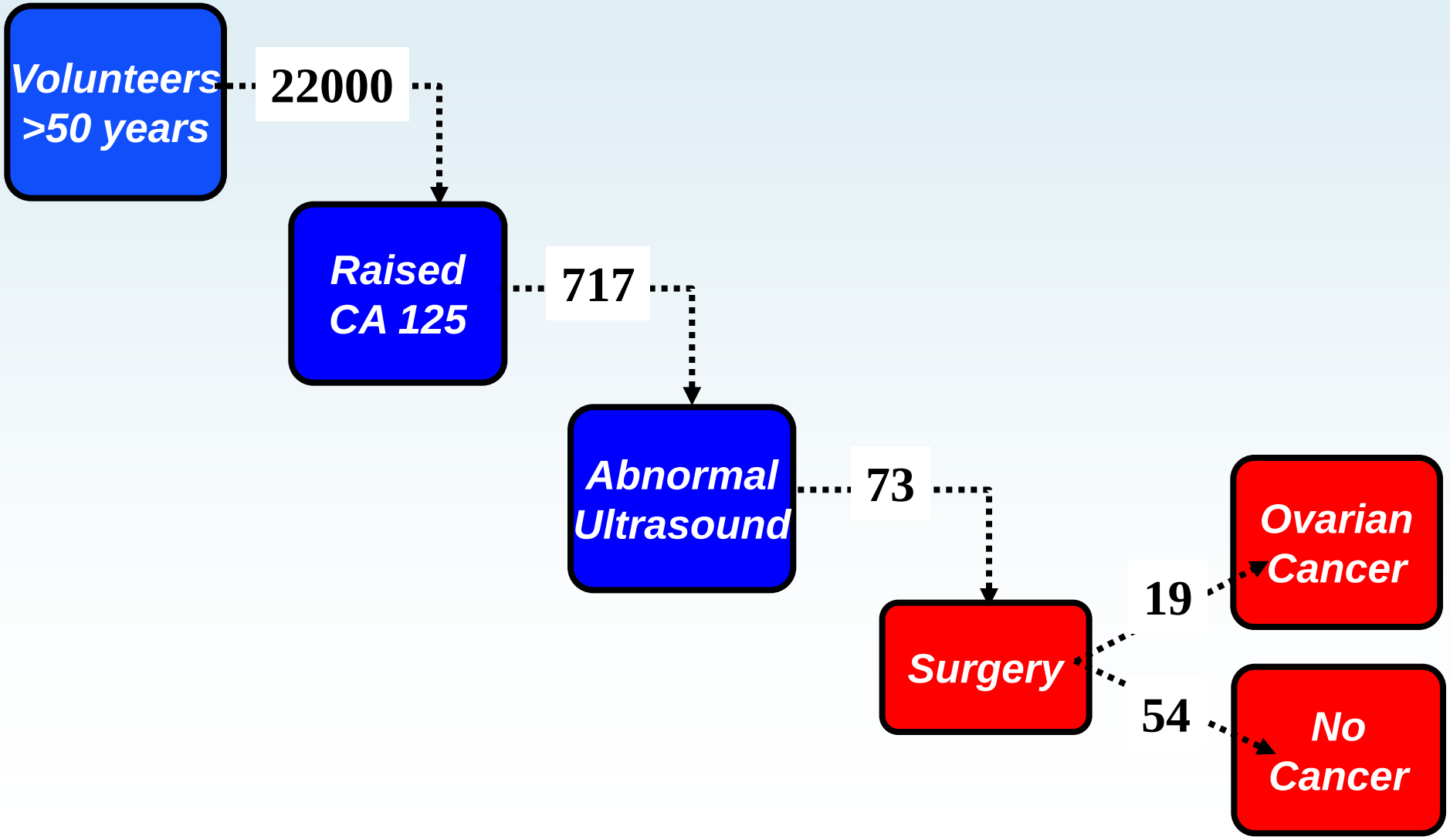
Performance of Ultrasound Screening



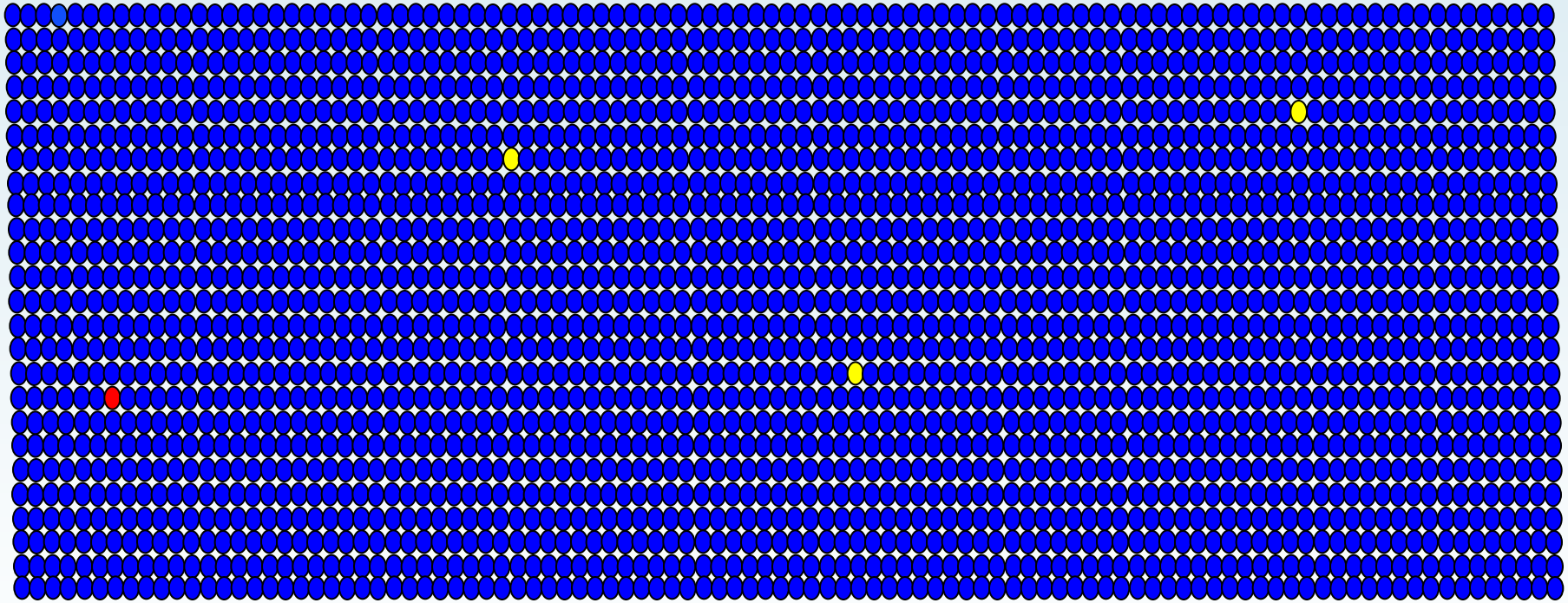
Advantages of using a Tumour Marker for 1º Screen

- Sampling is quick simple and can be performed anywhere
- Tests can be performed in one central lab
- Results objective + reproducible
- Cost per test relatively low

BART's A: MULTIMODAL SCREENING HAS A LOW FALSE POSITIVE RATE

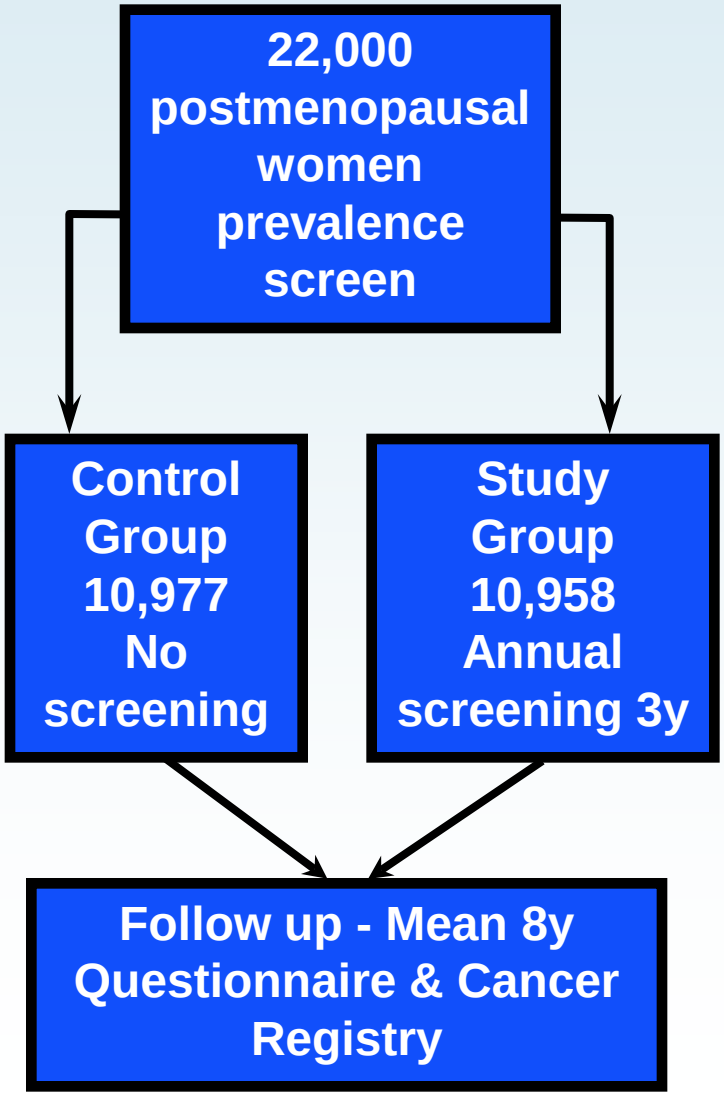


Multimodal Screening has a low false positive rate



3 unnecessary operations for each patient detected with ovarian cancer

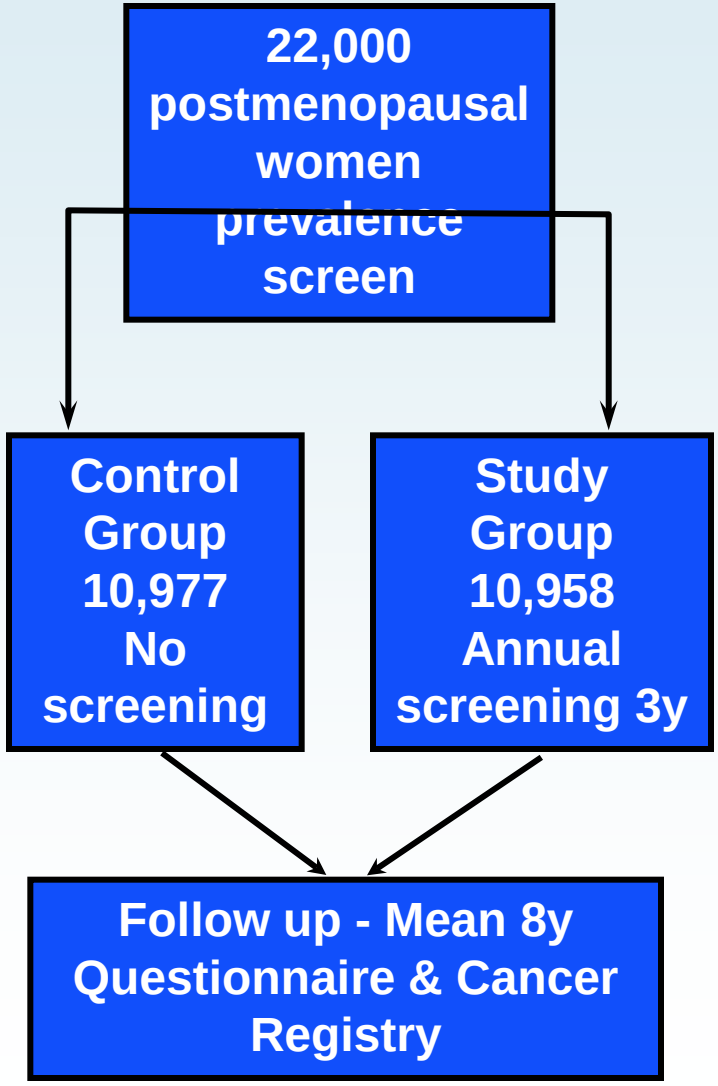
BART's B: Pilot Randomised Controlled Trial

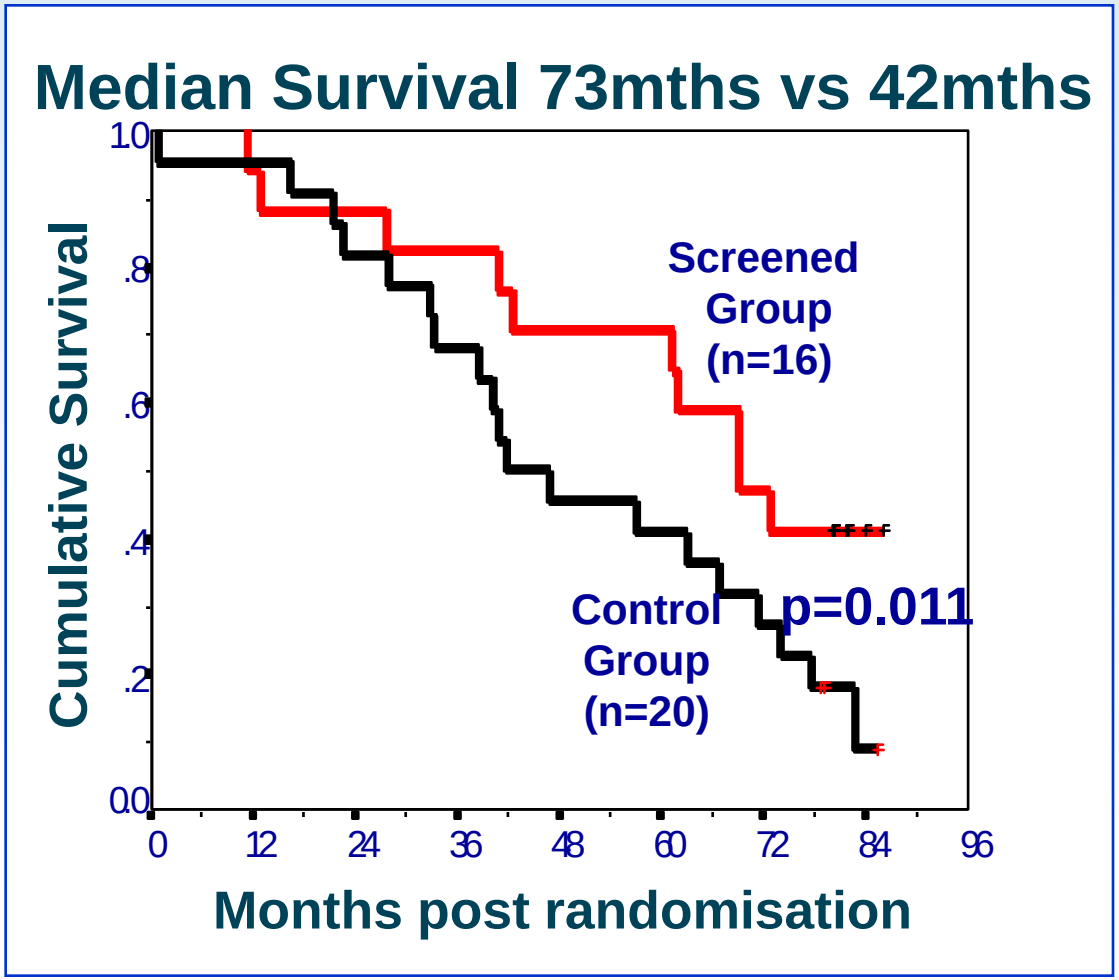


No differences between the control and study groups for:

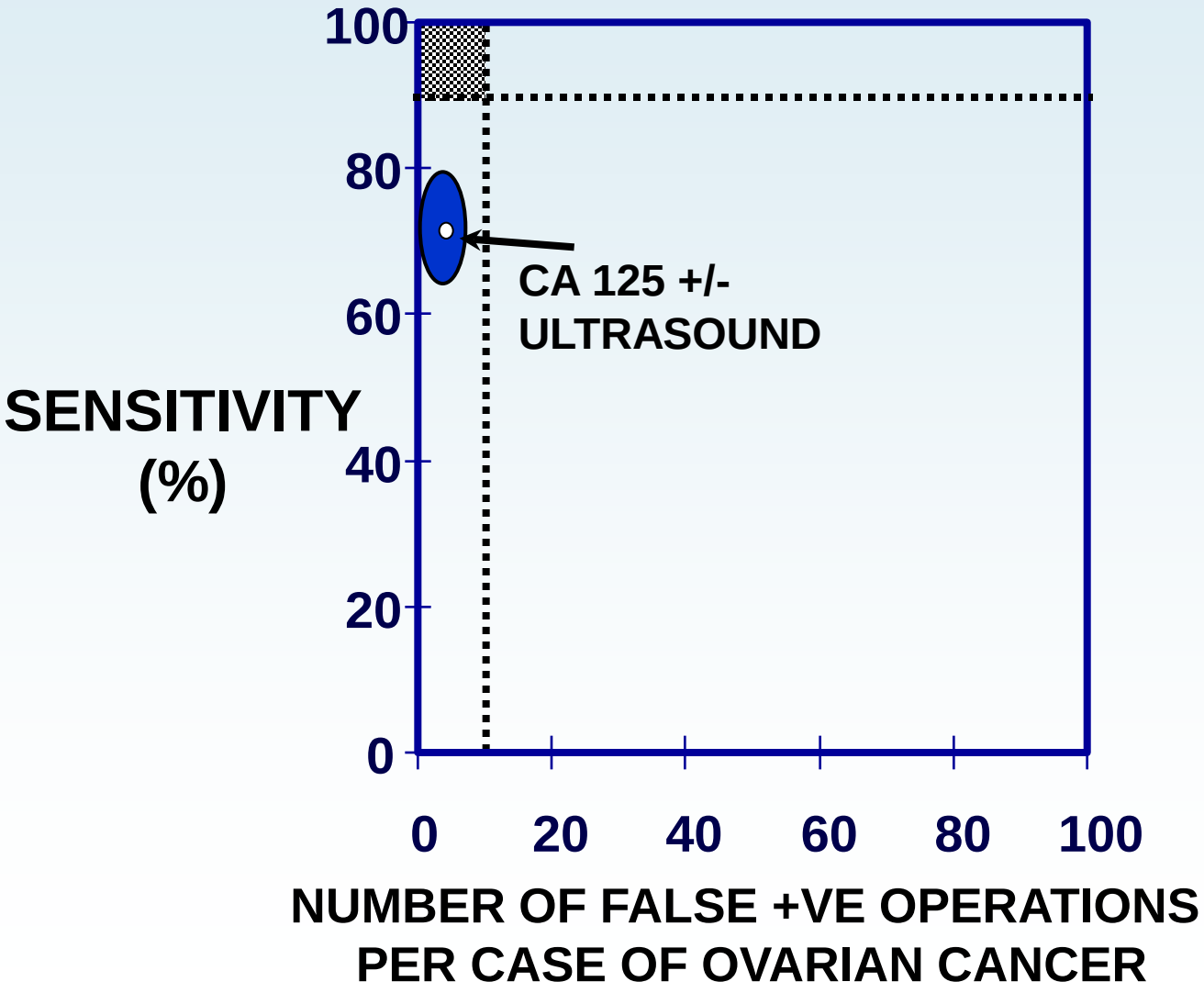
Age
Age at menarche
Age at menopause
Race
Parity
Smoking
OCP use
Family History
Histological type of OC
Prevalence screen result

Improved Survival in Screen Arm

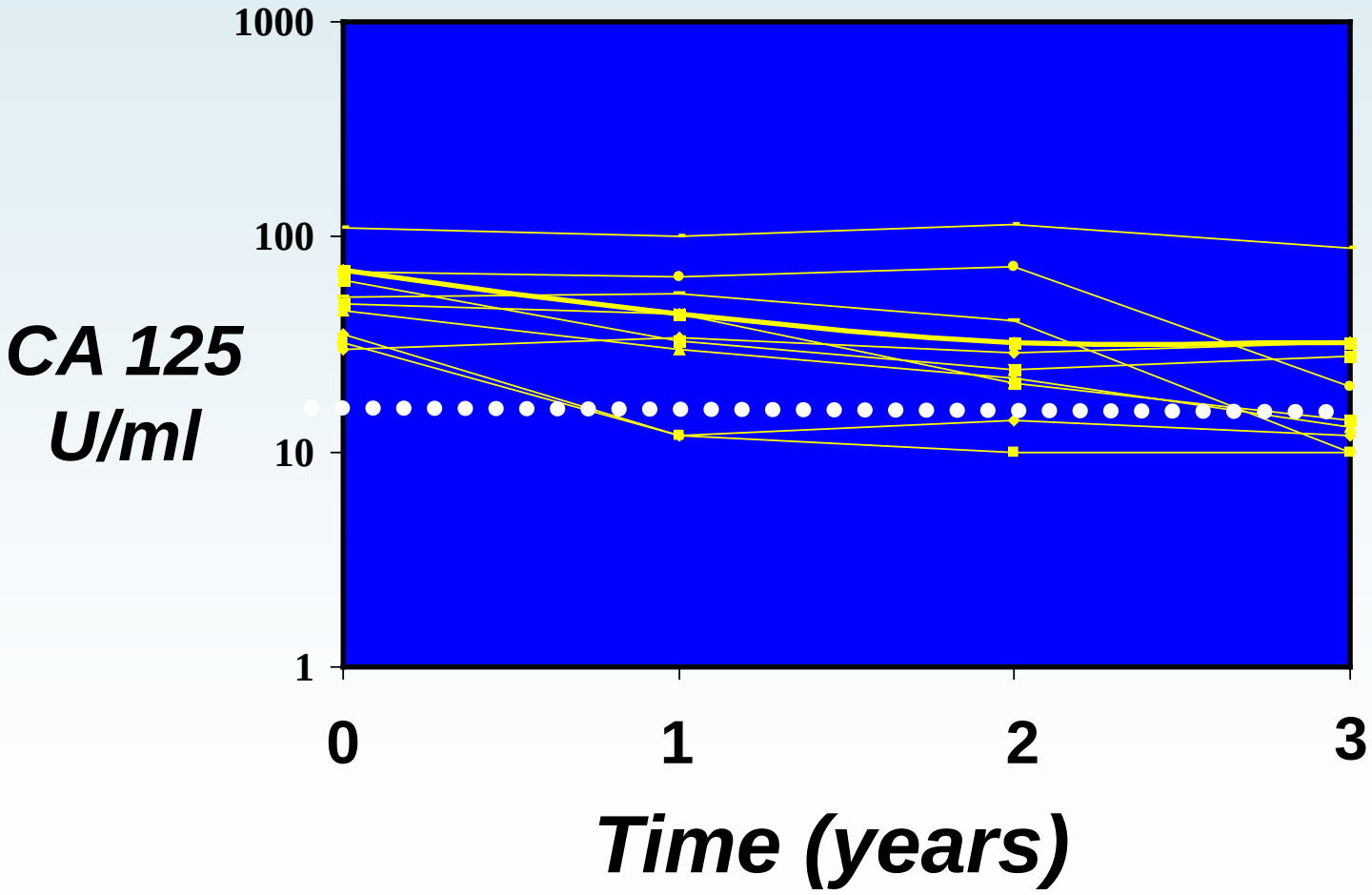




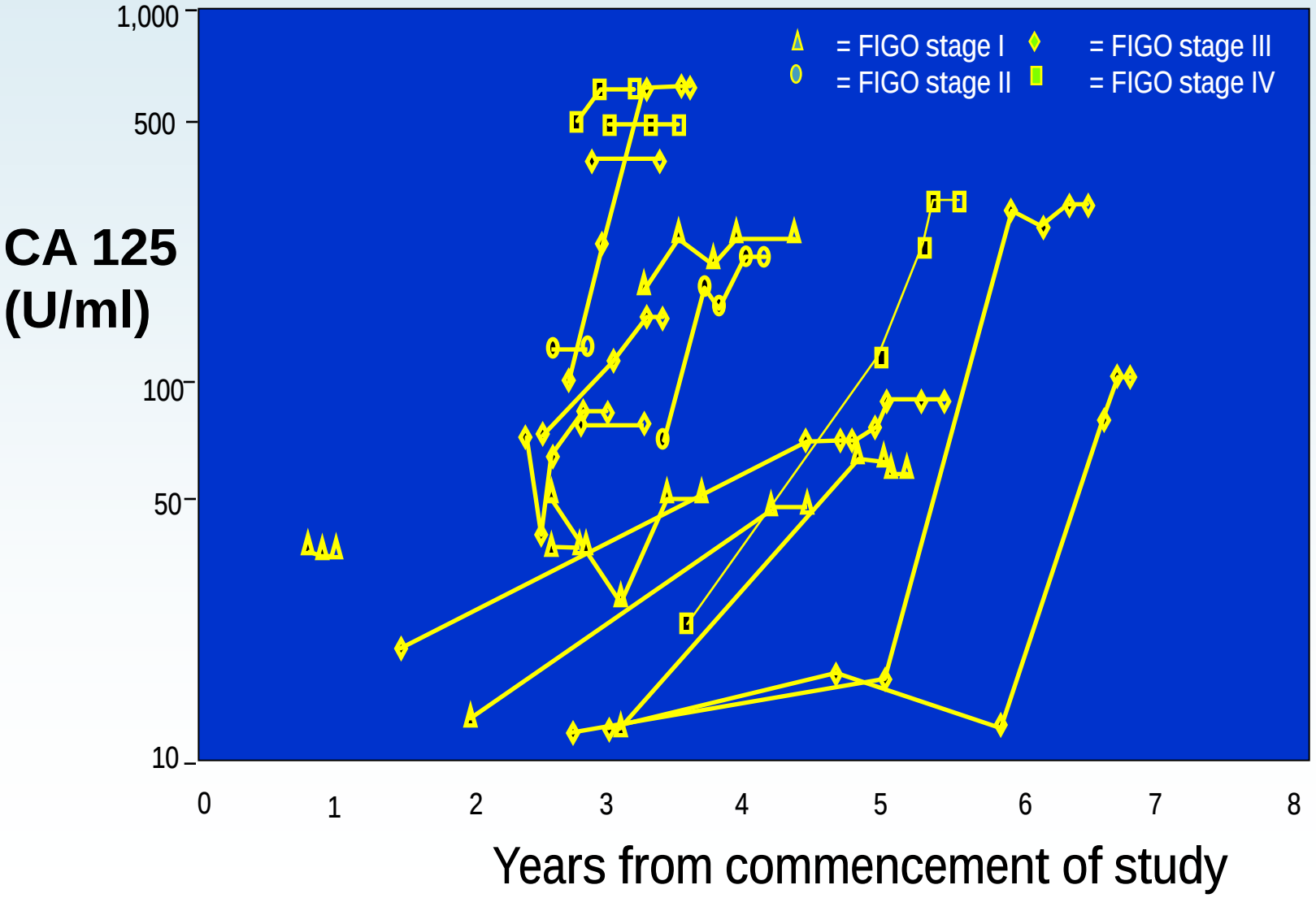
Sensitivity of CA 125 only 67% at 1 year



CA 125 in asymptomatic women with CA 125 >30



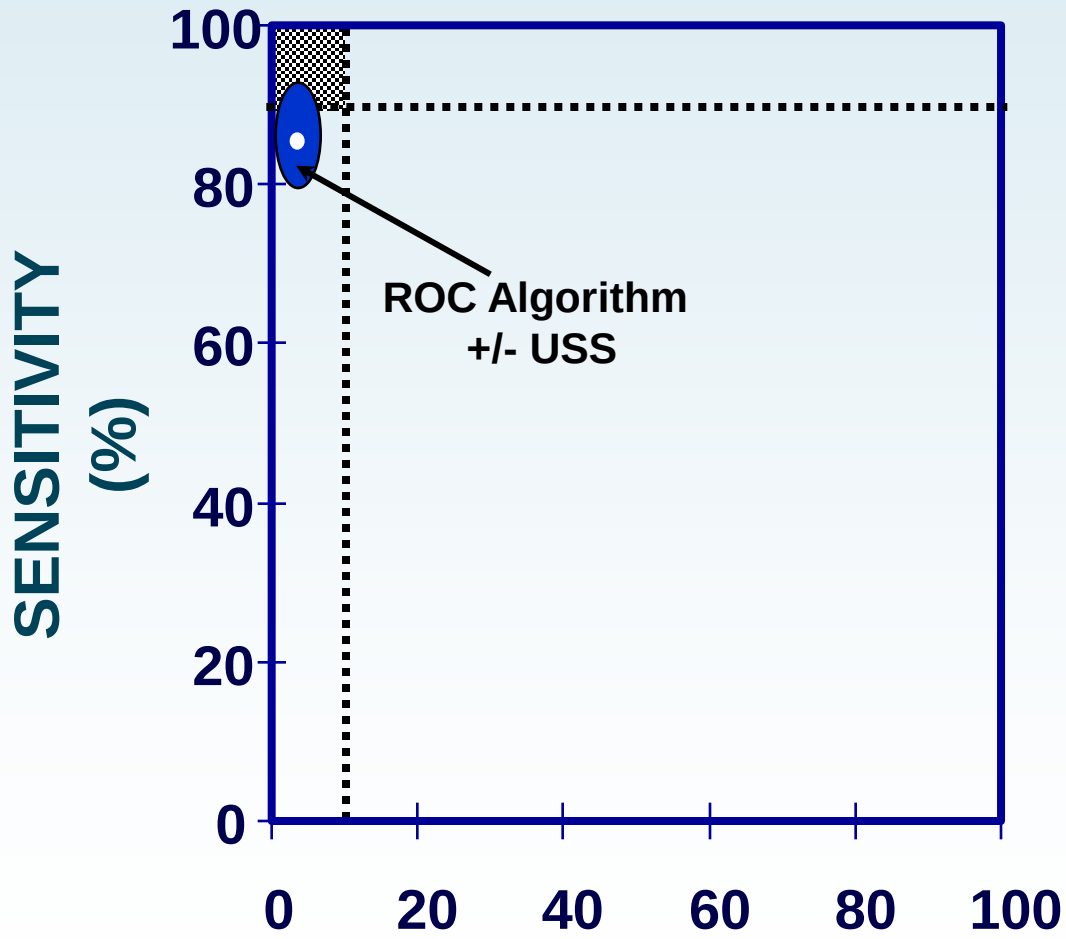
CA 125 in asymptomatic women with OC



Risk of Ovarian Cancer Algorithm (ROC)

- Computerised algorithm
- Compares each individual's CA125 profile to the pattern in ovarian cancer and healthy women.
- Closer the CA125 profile to known cases of ovarian cancer, the greater the risk of ovarian cancer
- Produces each individuals percentage risk of ovarian cancer during the next year

Performance of Risk of Ovarian Cancer Algorithm



Based on >50,000 screens Involving >30,000 Women Stockholm + Bart's A/B

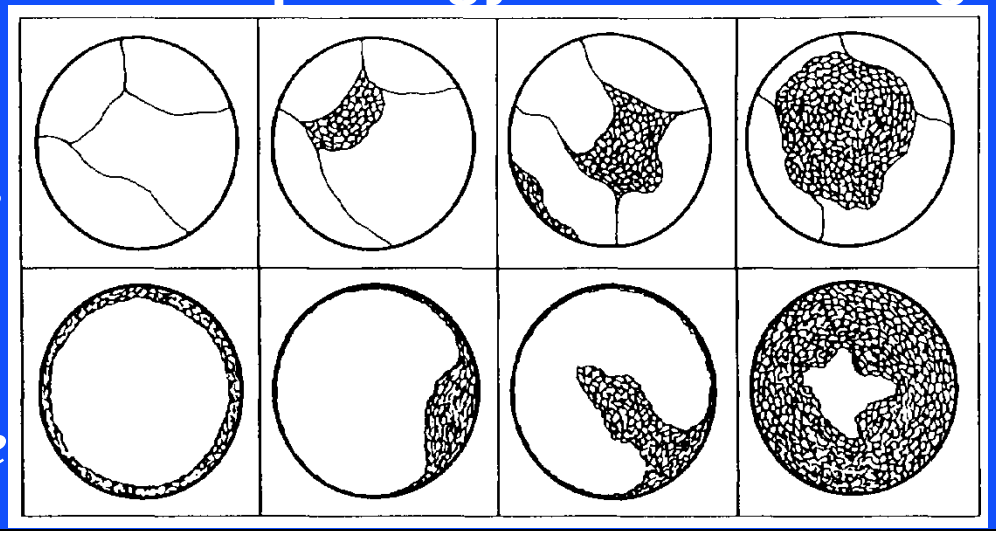
Skates, Menon, Jacobs et al JASA 2002, JCO 2003

Refinement of Ultrasound Screening strategy

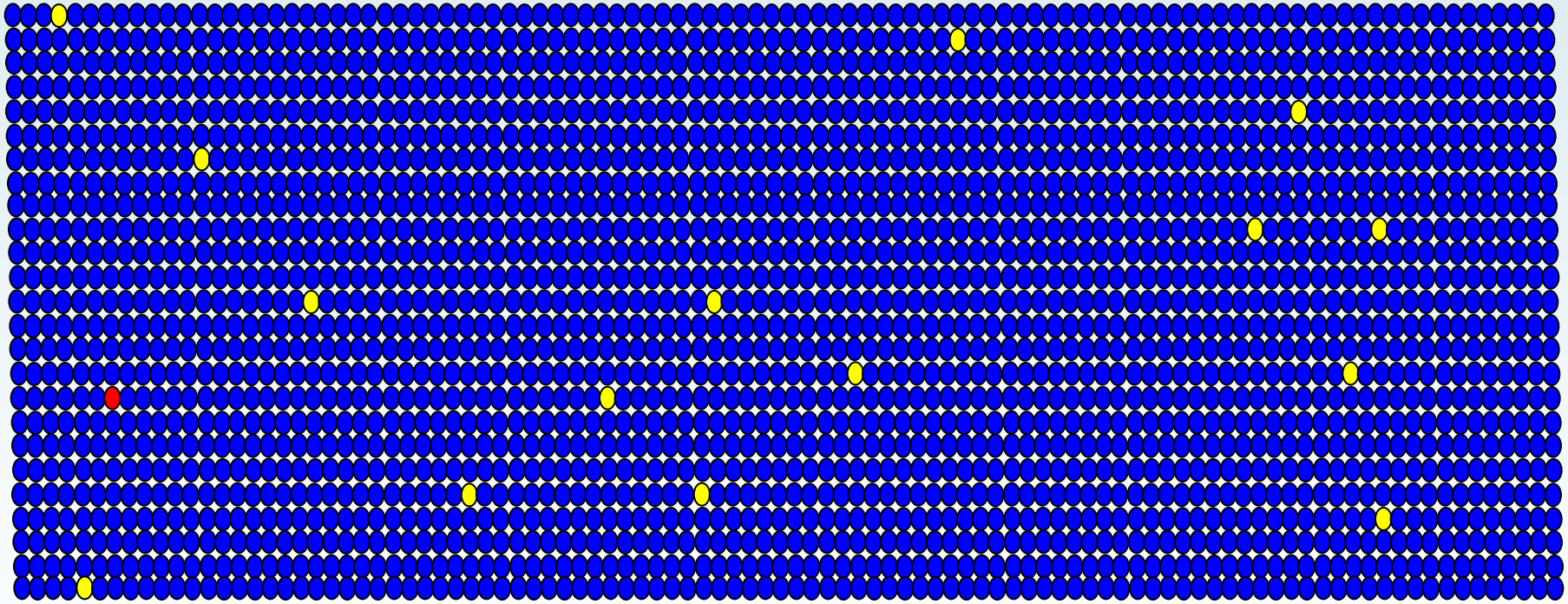
- TV rather than TA approach
- Sophisticated machines with high resolution
- Serial monitoring of abnormalities to document persistence/progression
- Recognition of low risk associated with unilocular anechoic ovarian cysts
- Development of morphology based scoring systems:

Septa structure

Wall structure

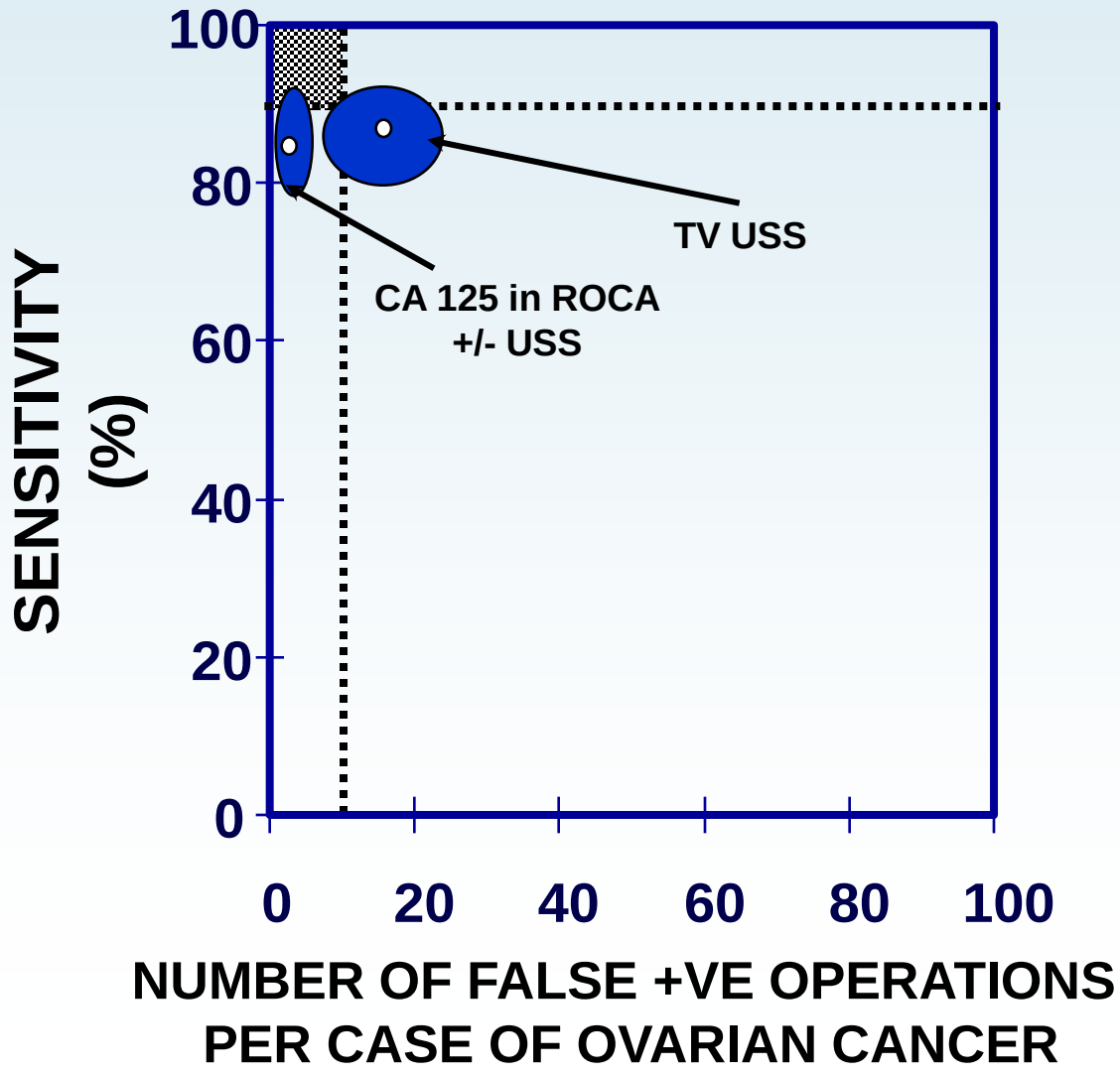


Refining Ultrasound Screening

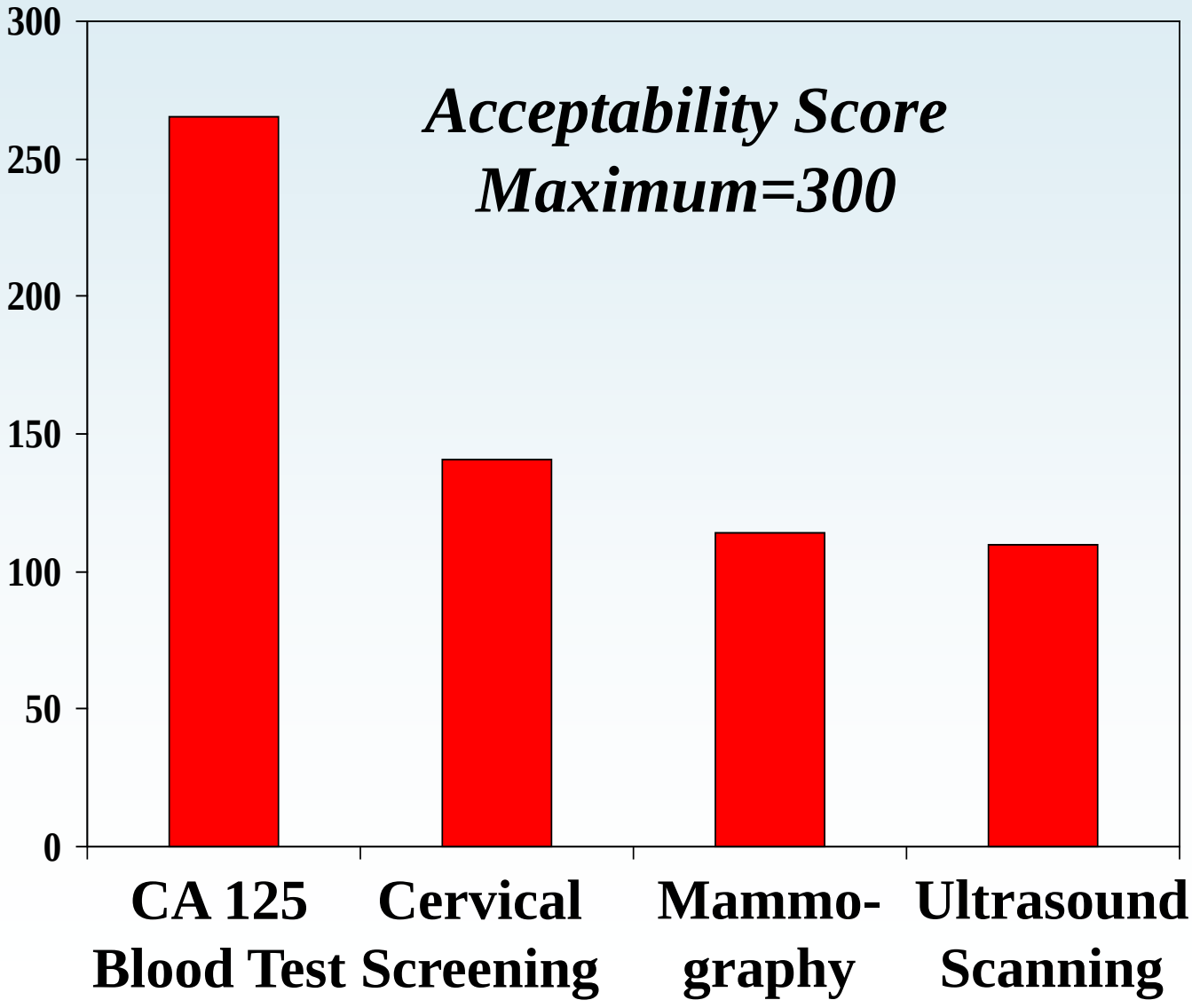


7-20 unnecessary operations for each patient detected with ovarian cancer

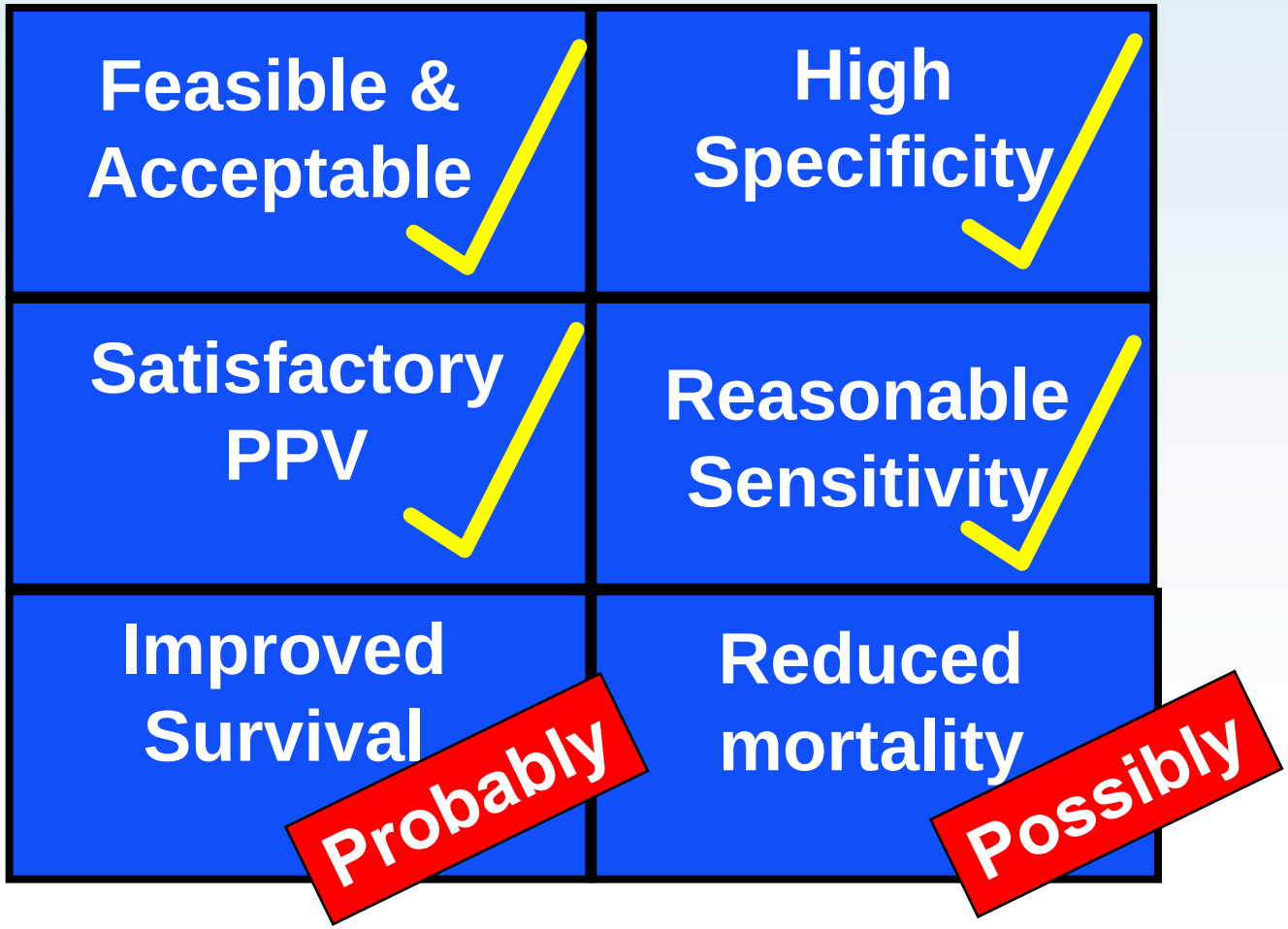
Performance of Screening Strategies for OC



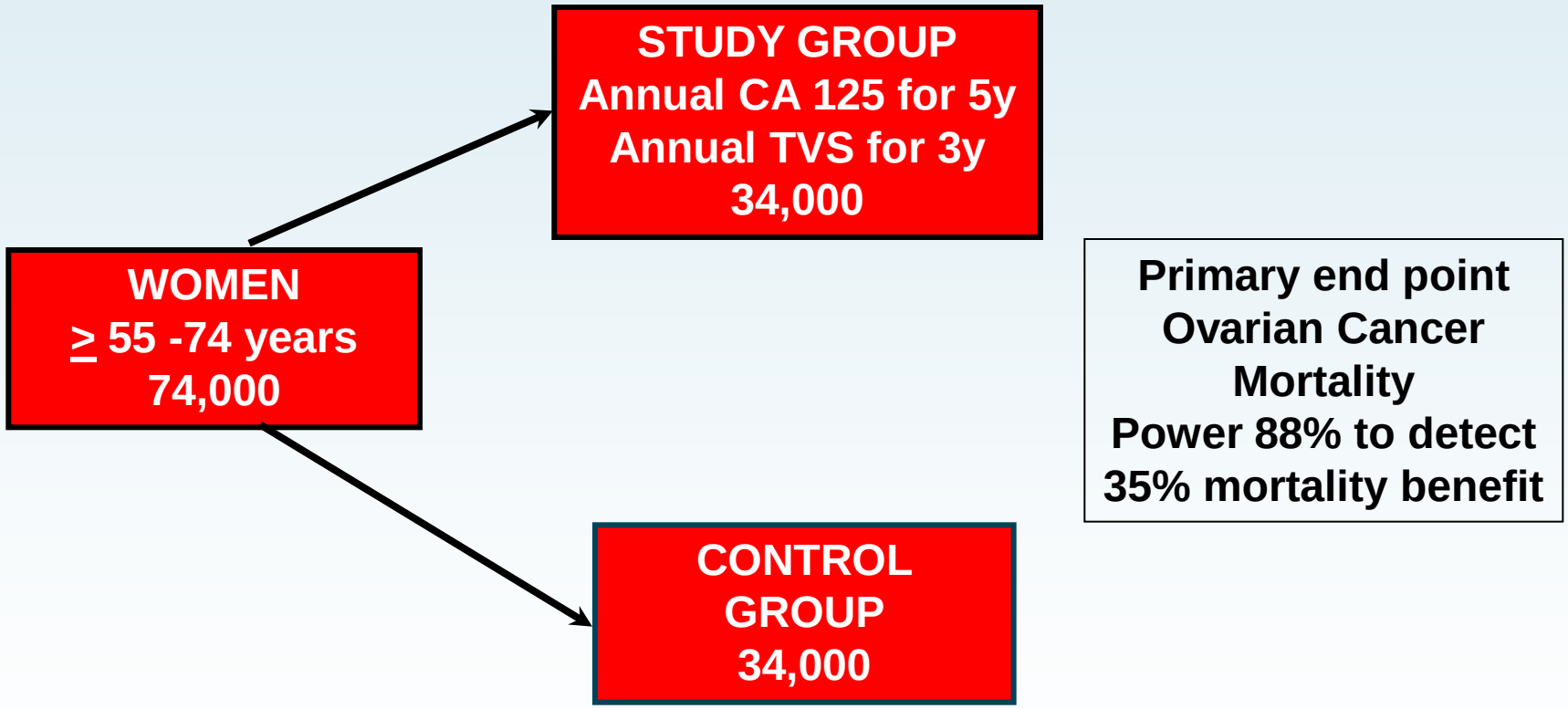
Screening is Acceptable to Women in the UK



STATUS OF POPULATION SCREENING FOR OVARIAN CANCER



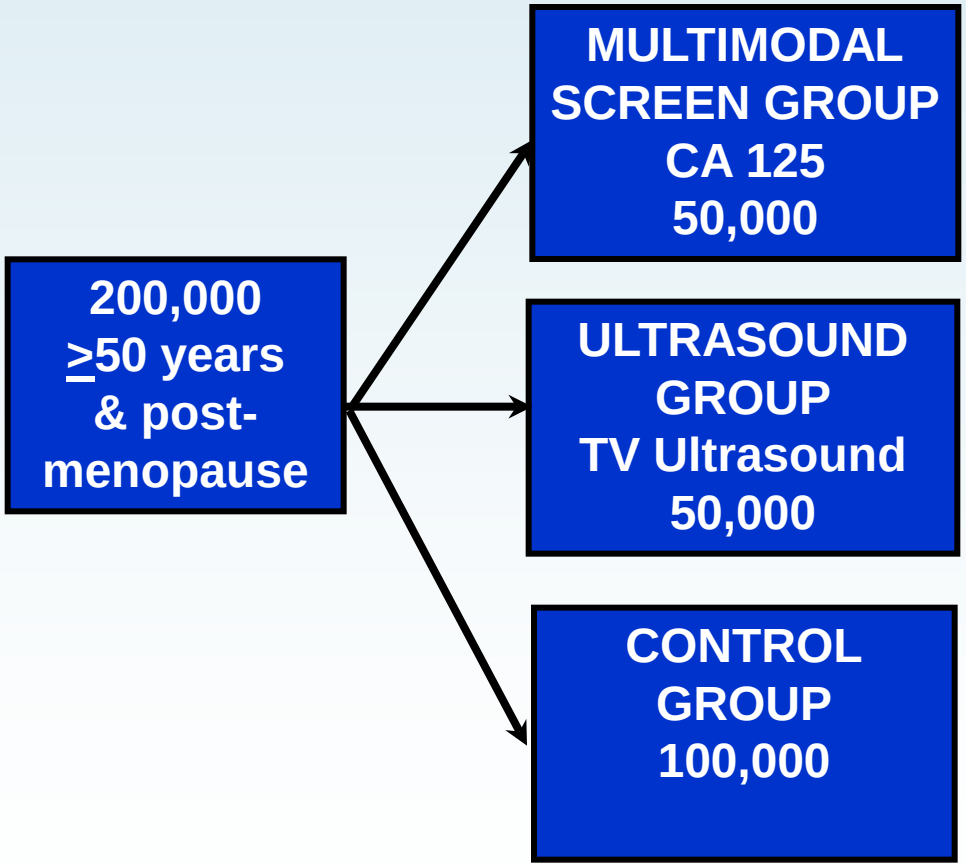
NIH PLCO (Prostate, Lung, Colorectal & Ovarian) Cancer Screening Trial



All women followed up for 13 years by postal questionnaire

UKCTOCS

UK Collaborative Trial of Ovarian Cancer Screening



OBJECTIVES

Primary:
Ovarian Cancer Mortality

Secondary:
Morbidity
Health Economics
Quality of Life
Acceptability
Compliance

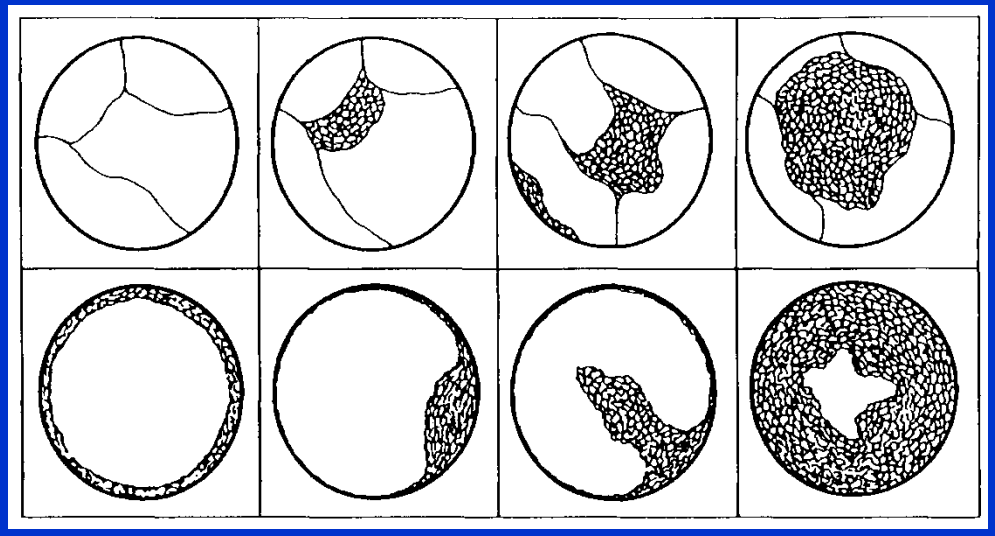
Additional:
Serum Bank

METHODS: USS Protocol

- Transvaginal Scanning
- Morphology based scoring systems:

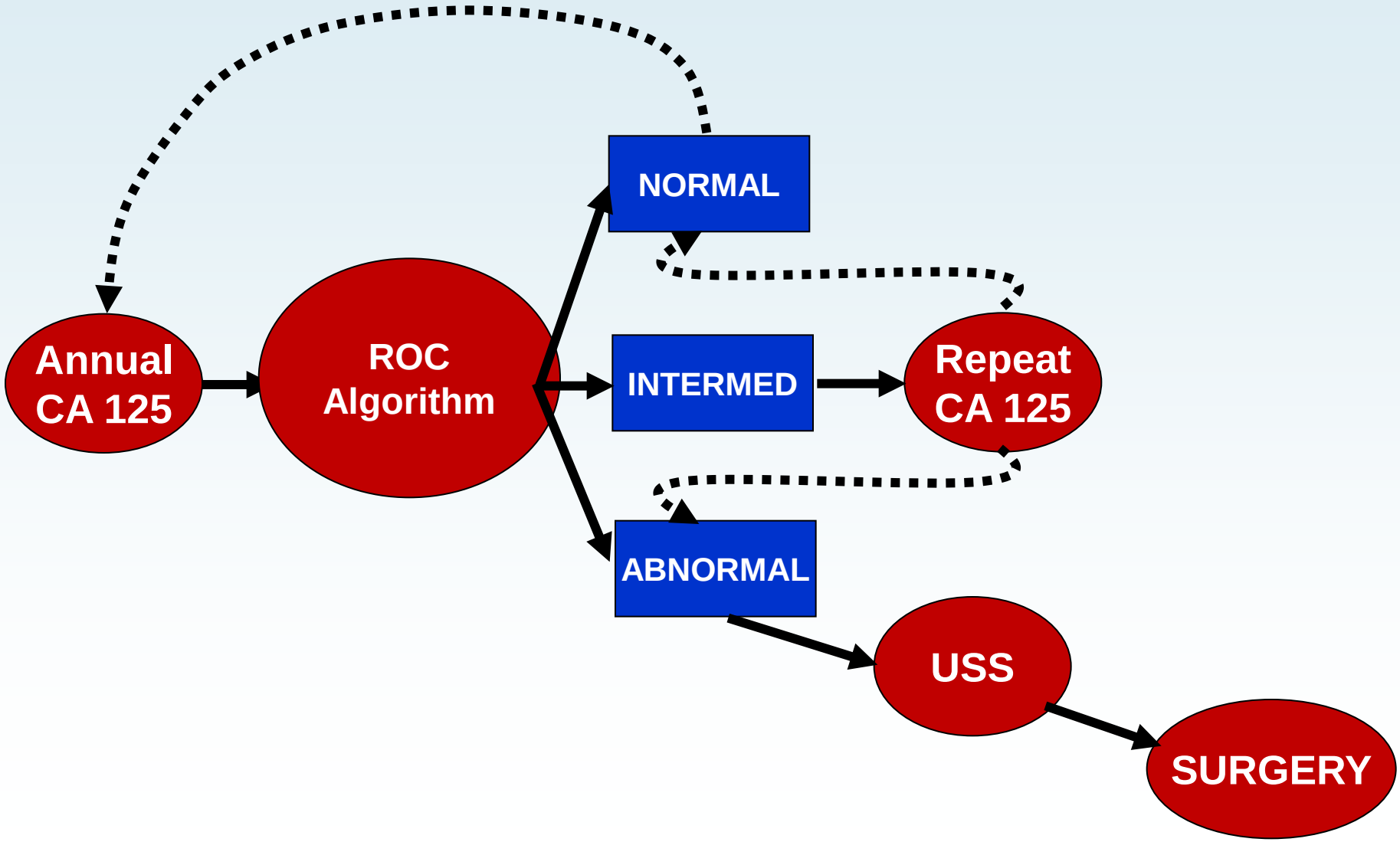
Septa structure

Wall structure



- Abnormal Level I screen – recall for Level II screen
- Abnormal Level II screen – referral Gyn onc opinion

METHODS: Multimodal Protocol



METHODS: Logistics

- 13 Centres
- 50 permanent staff and 95 USS
- 27 Primary Care Trusts
- 250 General Practitioners
- 200,000 consents
- 300,000 ultrasound screens
- 500,000 CA 125 tests + blood samples
- 600,000 results letters
- 1.2 million invitations

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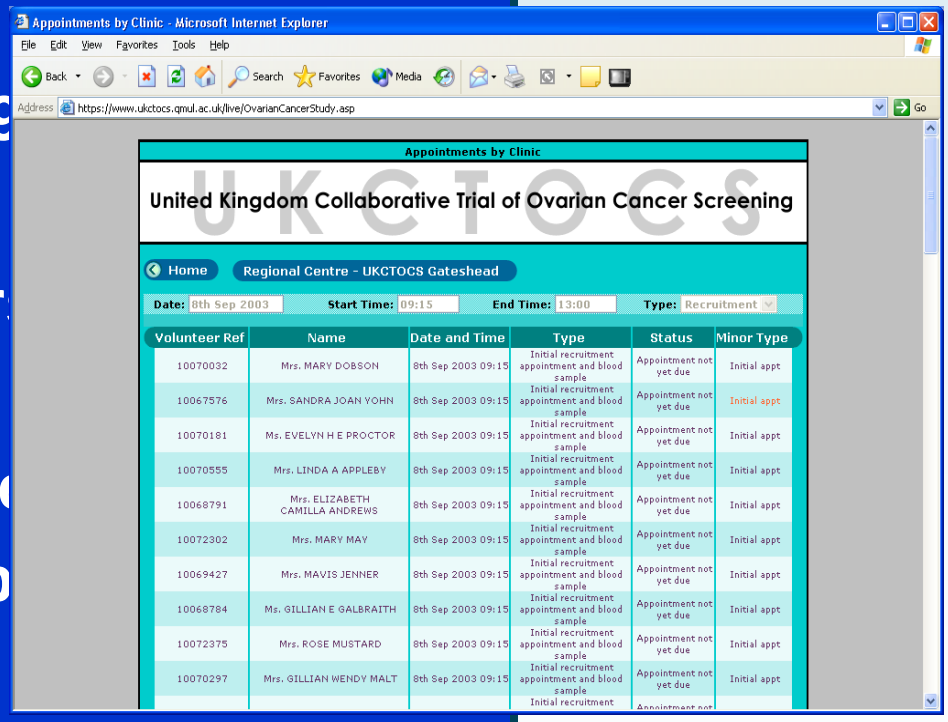


Web based / Image recognition/
Automation data entry, results, appointments

ACKNOWLEDGEMENTS

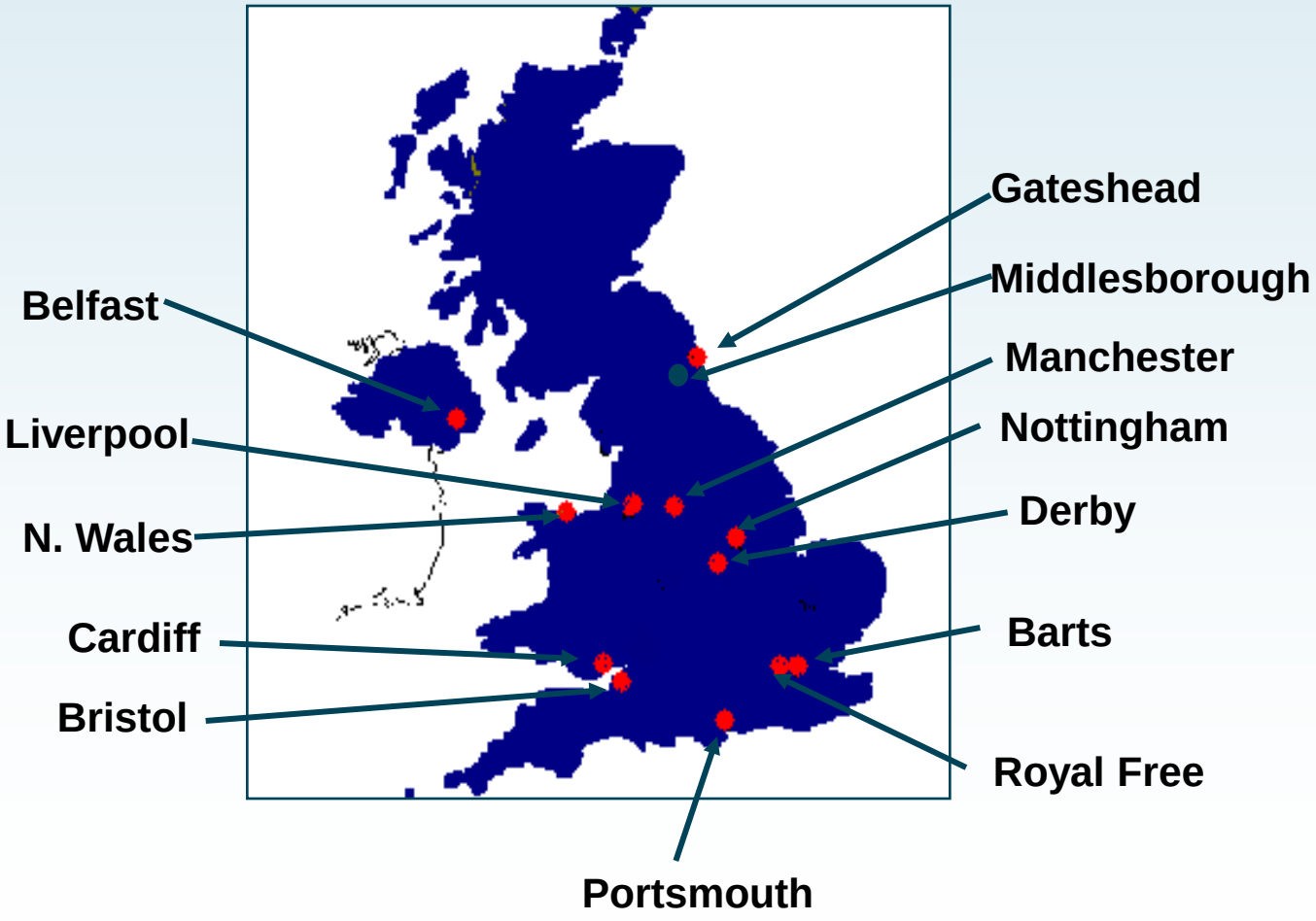
Co-Investigators

Usha Menon
Steven J Skates
James Mackay
Max Parmar
Lesley Fallowfield
Stuart Campbell

UKCTOCS + UKFOCSS Teams

Andy Ryan
Alex Gentry-Maharaj
Lindsay Fraser
Adam Rosenthal

UKCTOCS: Centres & Recruitment



ACKNOWLEDGEMENTS

UKCTOCS Collaborators

David Oram/K Reynolds (Bart's)
T Lopes/K Godfrey (Gateshead)
Karin Williamson (Nottingham)
Jonathon Herod (Liverpool)
Robert Woolas (Portsmouth)
Tim Mould (Royal Free)
John Murdoch (Bristol)
Mourad Seif (Manchester)
Nazar Amso (Cardiff)
Simon Leeson (Bangor)
Stephen Dobbs (Belfast)
Ian Scott (Derby)
Derek Cruickshank (Middlesboro)

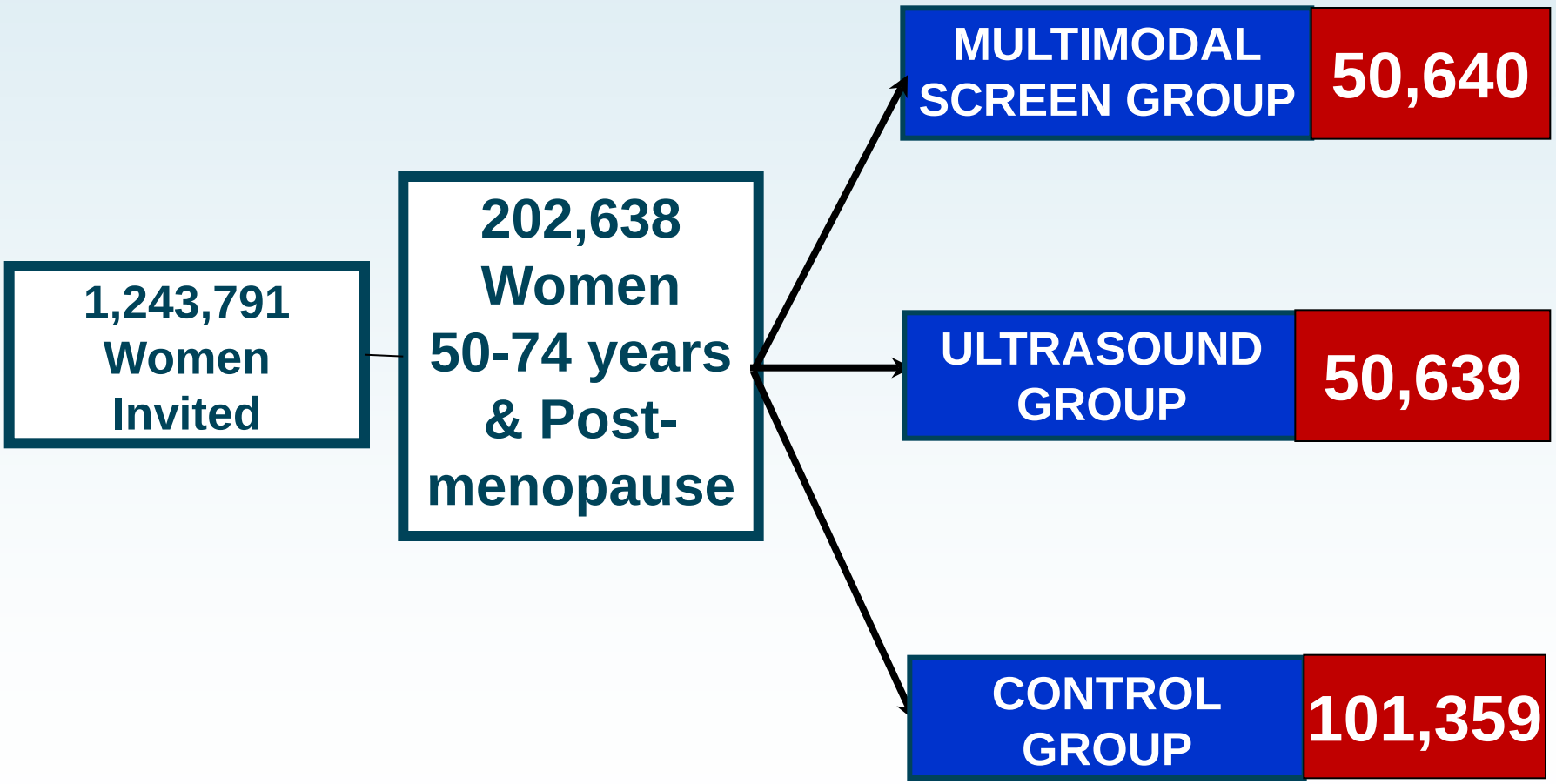
UKFOCSS Collaborators

Robin Crawford (Cambridge)
CB Lynch (Milton Keynes)
Josephine McHugo (Birmingham)
Omar Freitas (Singleton)
Diana Eccles (Southampton)
Shirley Hodgson (St Georges)
Andy Nordin (Kent)
Robert Anderson (St Michaels)
Cyril Chapman (Birmingham)
Huw Dorkins (Northwick Park)
Fiona Douglas (Inst Hum Gen)
Ian Scott (Derby)
Carol Brewer (Exeter)
Gareth Evans (Manchester)

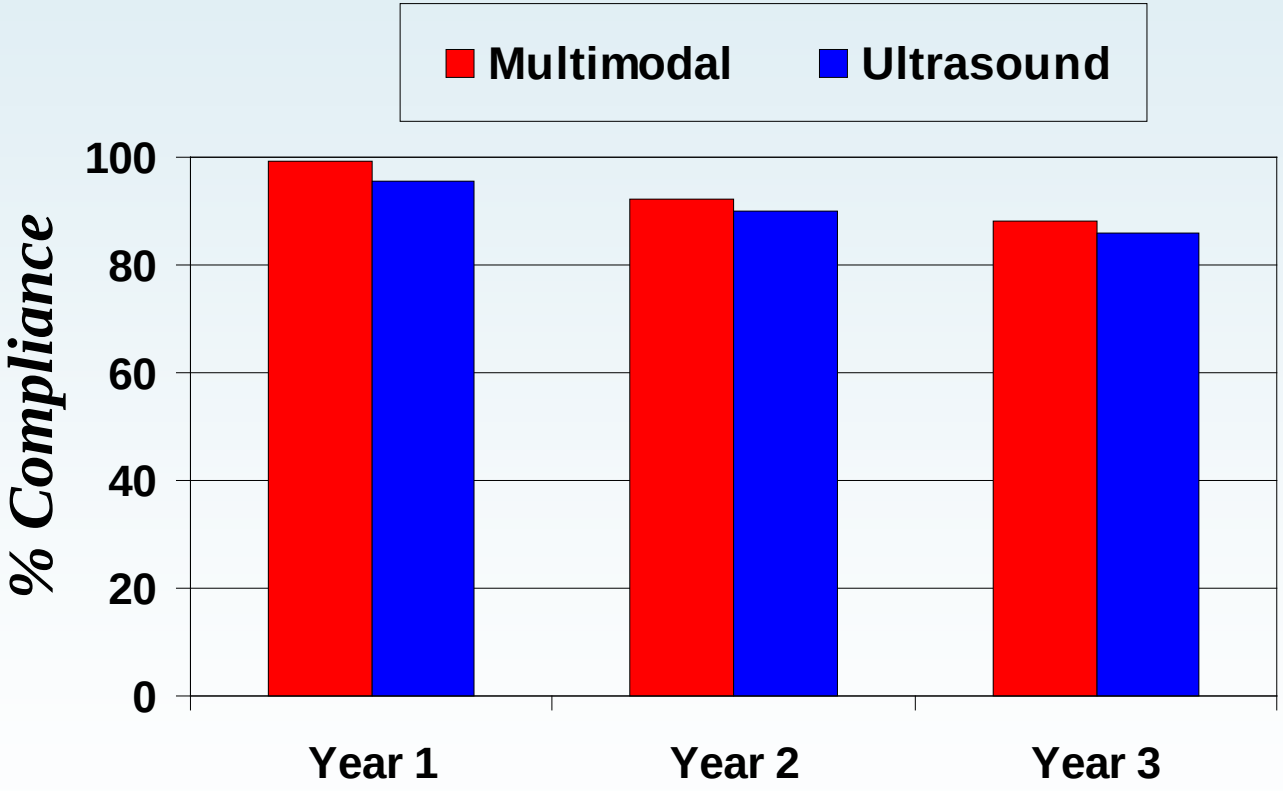
International Collaborators

Bob Bast
Nicole Urban
Dan Cramer
Bob Knapp
Uzi Beller
Andy Berchuck
Zhen Zhang
Susanne Kjaer
Anna Lokshin

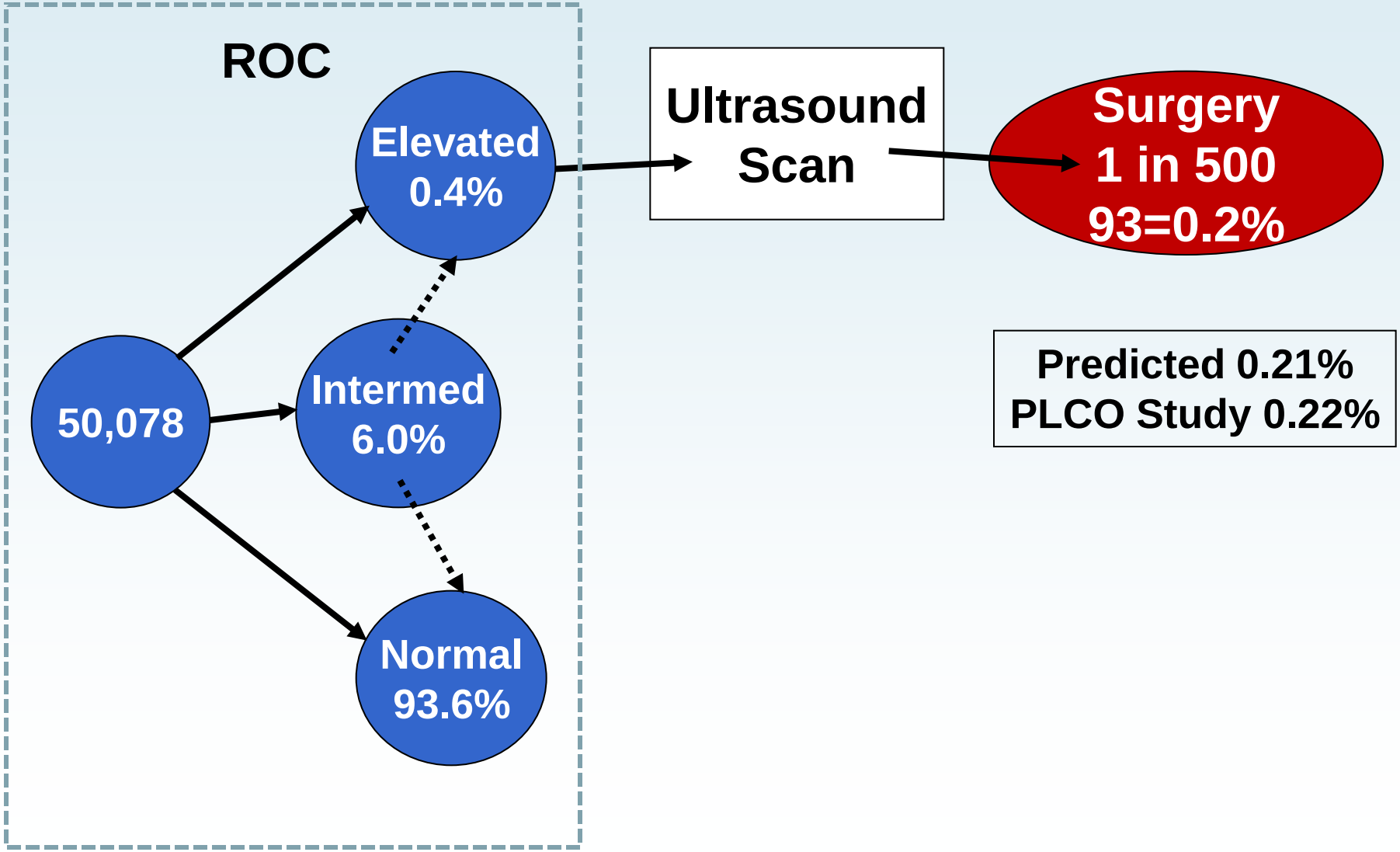
UKCTOCS: Randomisation



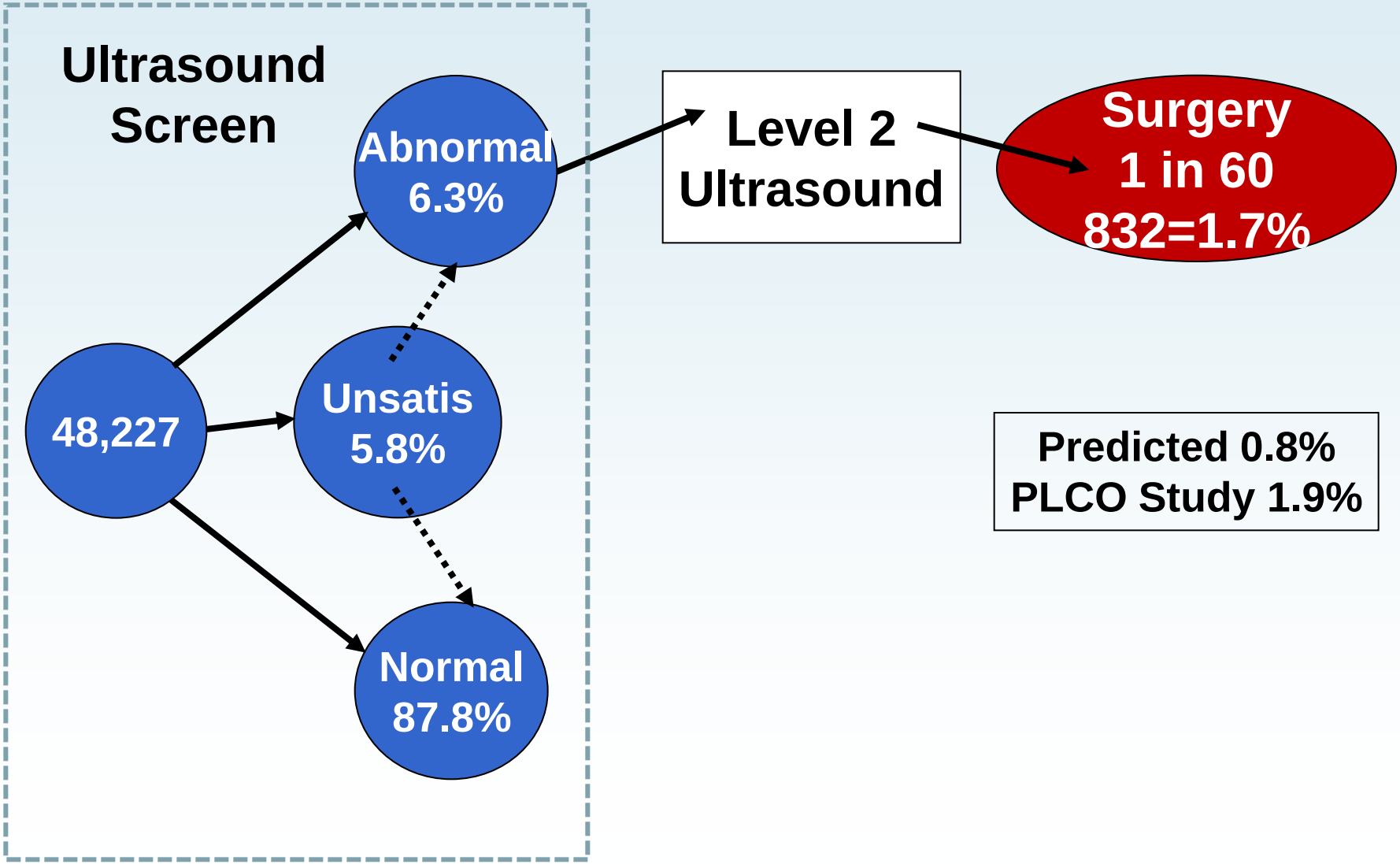
UKCTOCS: Screening Compliance



UKCTOCS: Multimodal Screening



UKCTOCS: Ultrasound Screening



UKCTOCS: Pathology in Screen Positives

Histopathology	Multimodal N=97	Ultrasound N=845
Normal	0	15
Benign	40	732
Borderline	8	20
Non Epith Ov	0	1
Non-Ov Cancer	7	12
Primary Invasive Cancer Ovary or Fallopian Tube	34	24

UKCTOCS: Test Sensitivity

Primary Invasive Cancer Ovary or Fallopian Tube	Multimodal Arm	Ultrasound Arm
Screen Detected at Prevalence Screen	34	24
Screen Negative at 1 year follow up	4	8
Apparent Sensitivity	89.5% (34/38)	75.0% (24/32)

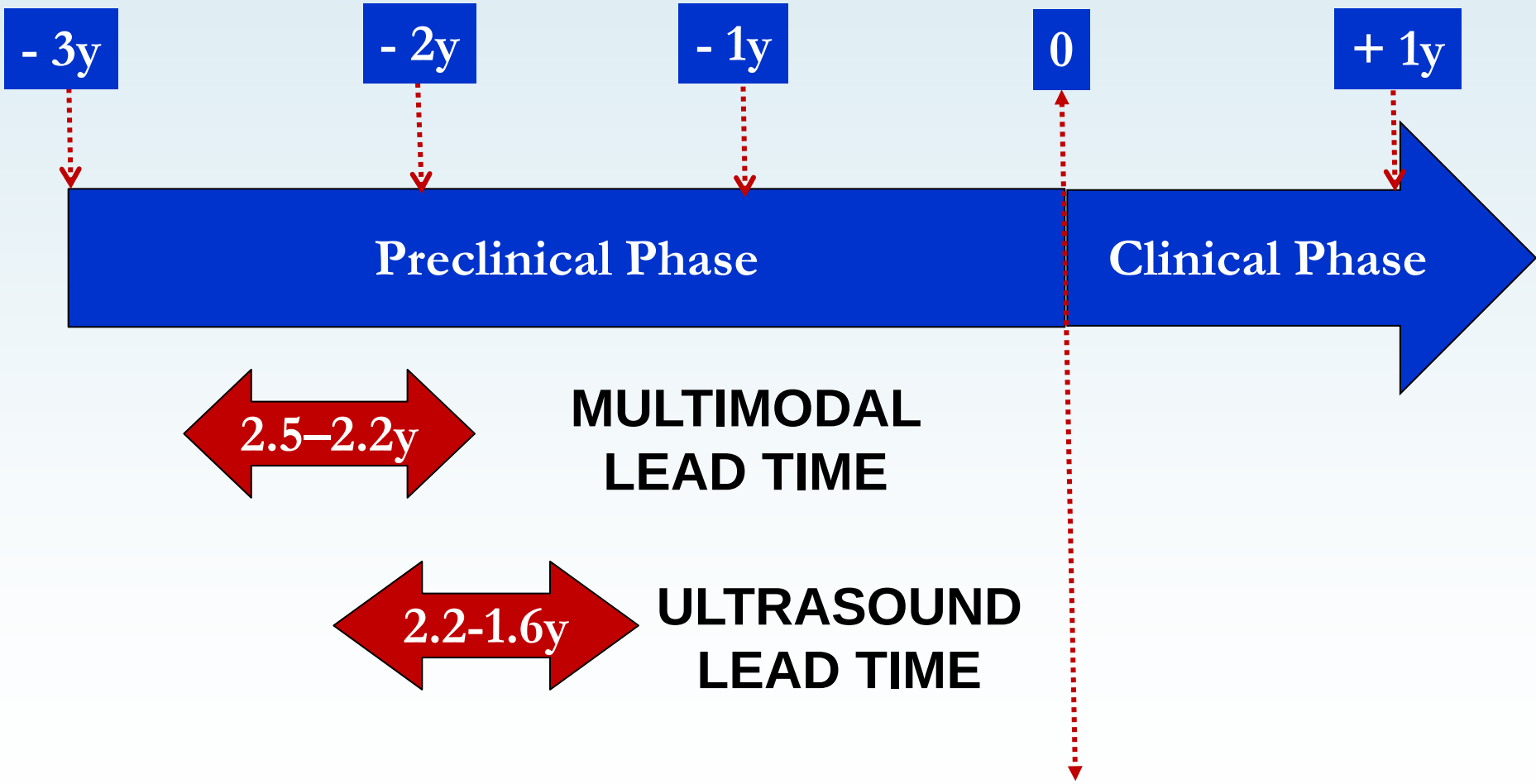
UKCTOCS: Test Sensitivity

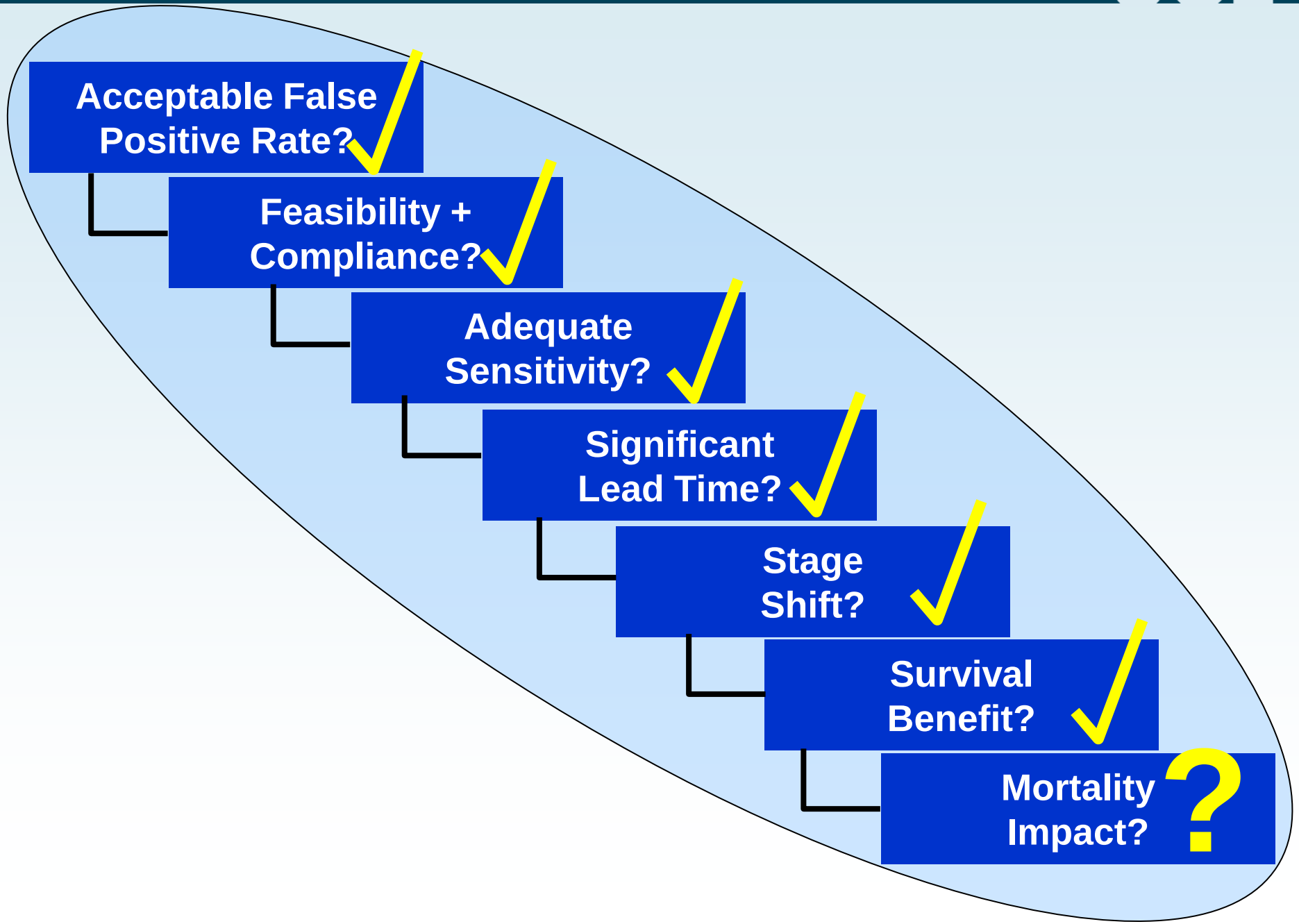
Primary Invasive Cancer Ovary or Fallopian Tube	Multimodal Arm	Ultrasound Arm
Screen Detected at Prevalence Screen	34	24
Screen Negative at 1 year follow up	4	8
Apparent Sensitivity	89.5% (34/38)	75.0% (24/32)
PLCO	51.7%	67.4%

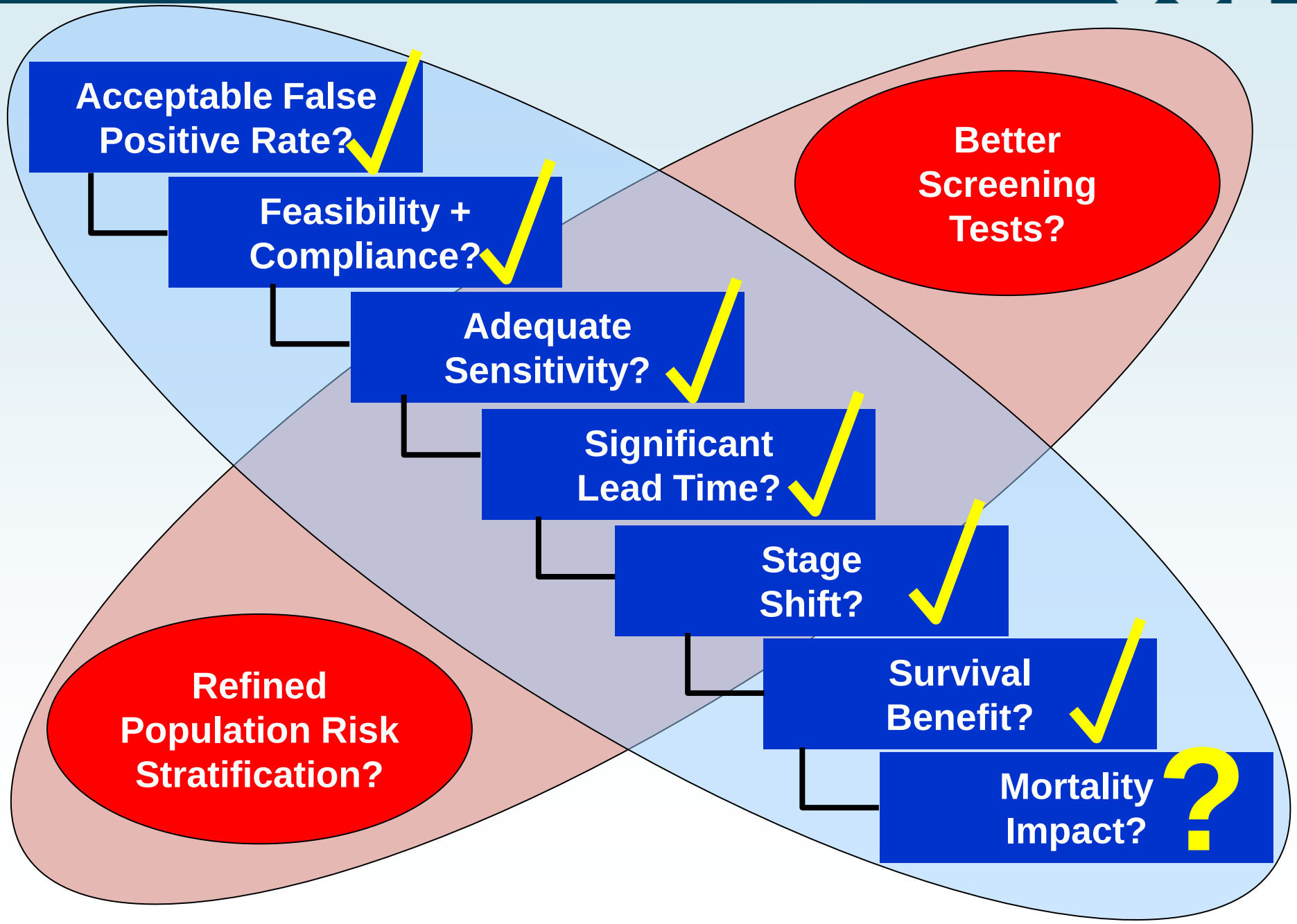
UKCTOCS: Stage distribution of Screen detected cancers

Stage	M	U
I	14	9
II	2	2
III	16	10
IV	0	1
Not staged	1	1
Early stage (I/II) %	48.50%	47.80%
PLCO	15%	28%

UKCTOCS: Estimating Lead Time




Acceptable False Positive Rate?
Feasibility + Compliance?
Adequate Sensitivity?
Significant Lead Time?
Stage Shift?
Survival Benefit?
Mortality Impact?
?


Acceptable False Positive Rate?
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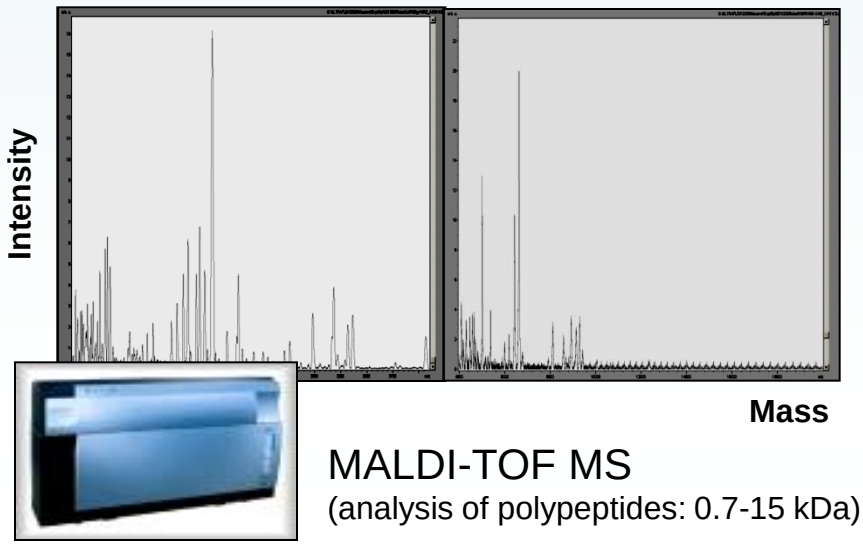
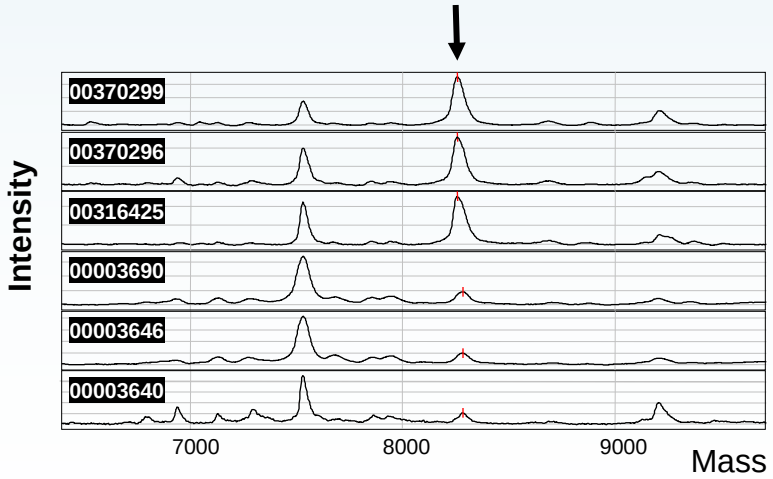
Significant Lead Time?
Stage Shift?
Survival Benefit?
Mortality Impact?
?
Better Screening Tests?
Refined Population Risk Stratification?

Biomarker discovery

- Serum may be a unique, non-invasive source of cancer markers: tumours shed proteins into the bloodstream
- To generate and compare proteomic patterns of serum from healthy donors, cases of ovarian cancer and from individuals prior to diagnosis (UKCTOCS/UKOPS)
- Link HTP fractionation strategies (using robotics) to MS-based profiling

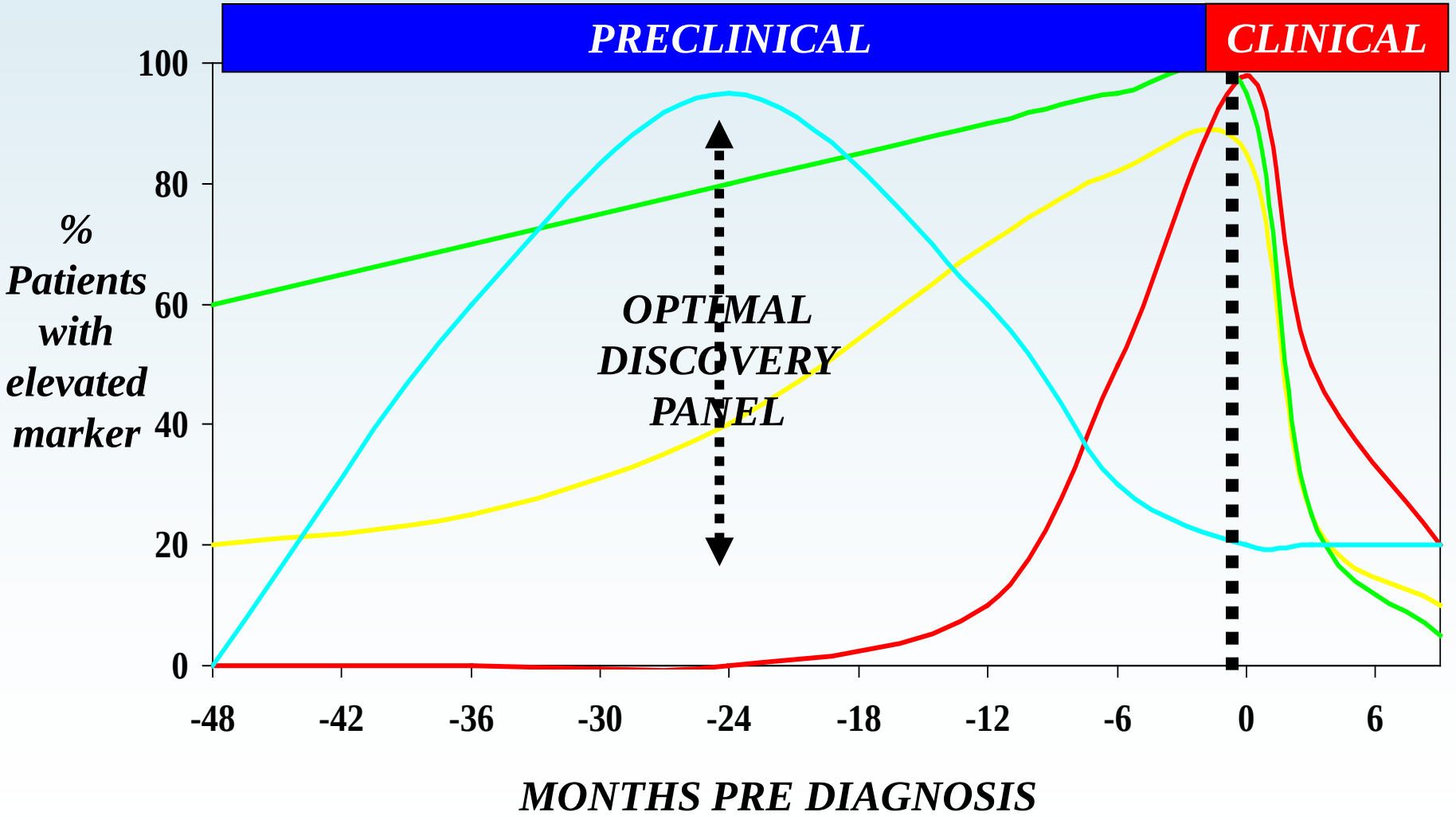


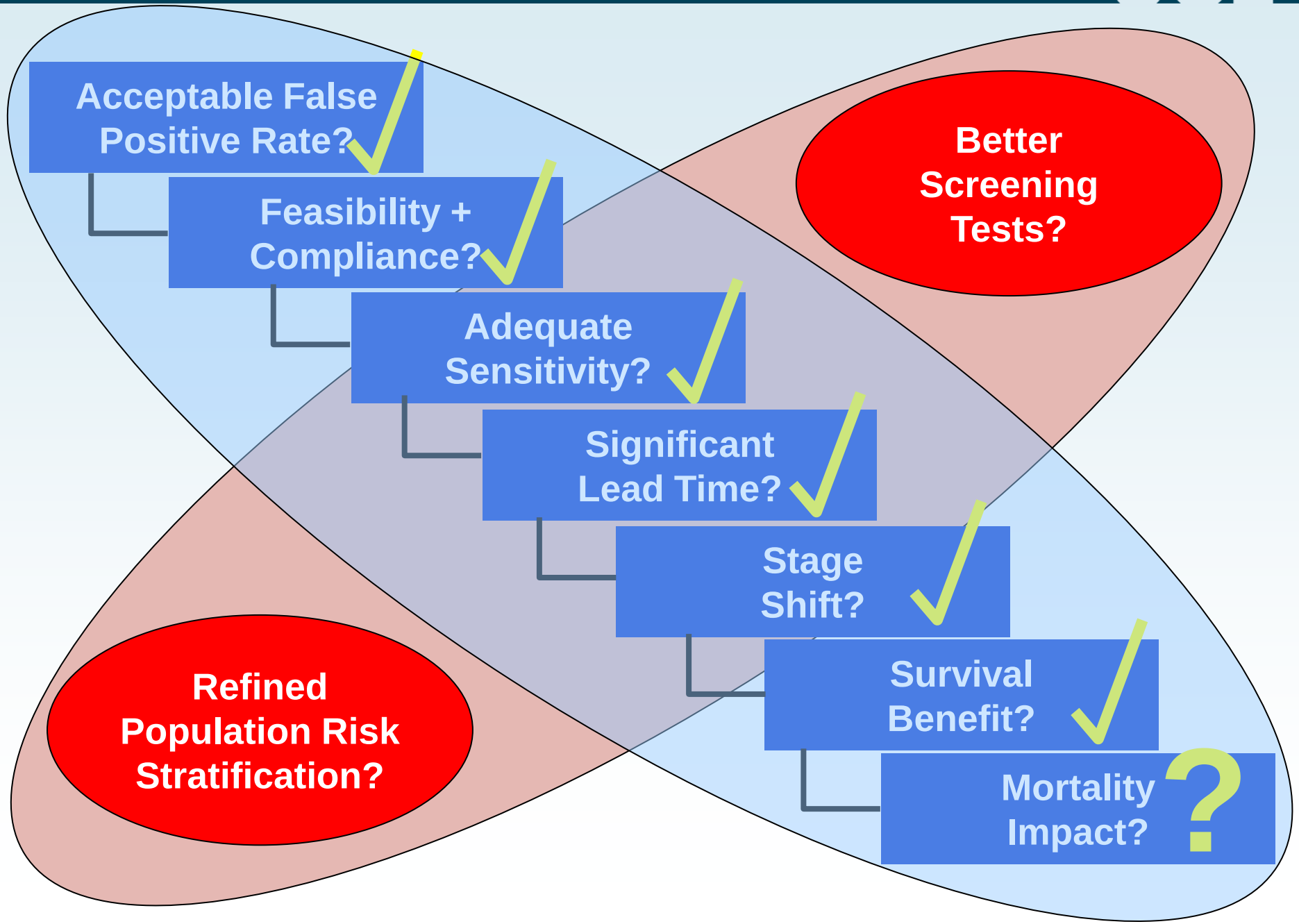
MALDI-TOF MS
(analysis of polypeptides: 0.7-15 kDa)



SELDI-TOF MS
(analysis of proteins: 2.5-200 kDa)

BIOMARKERS WITH GREATER SENSITIVITY & LEAD TIME

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