



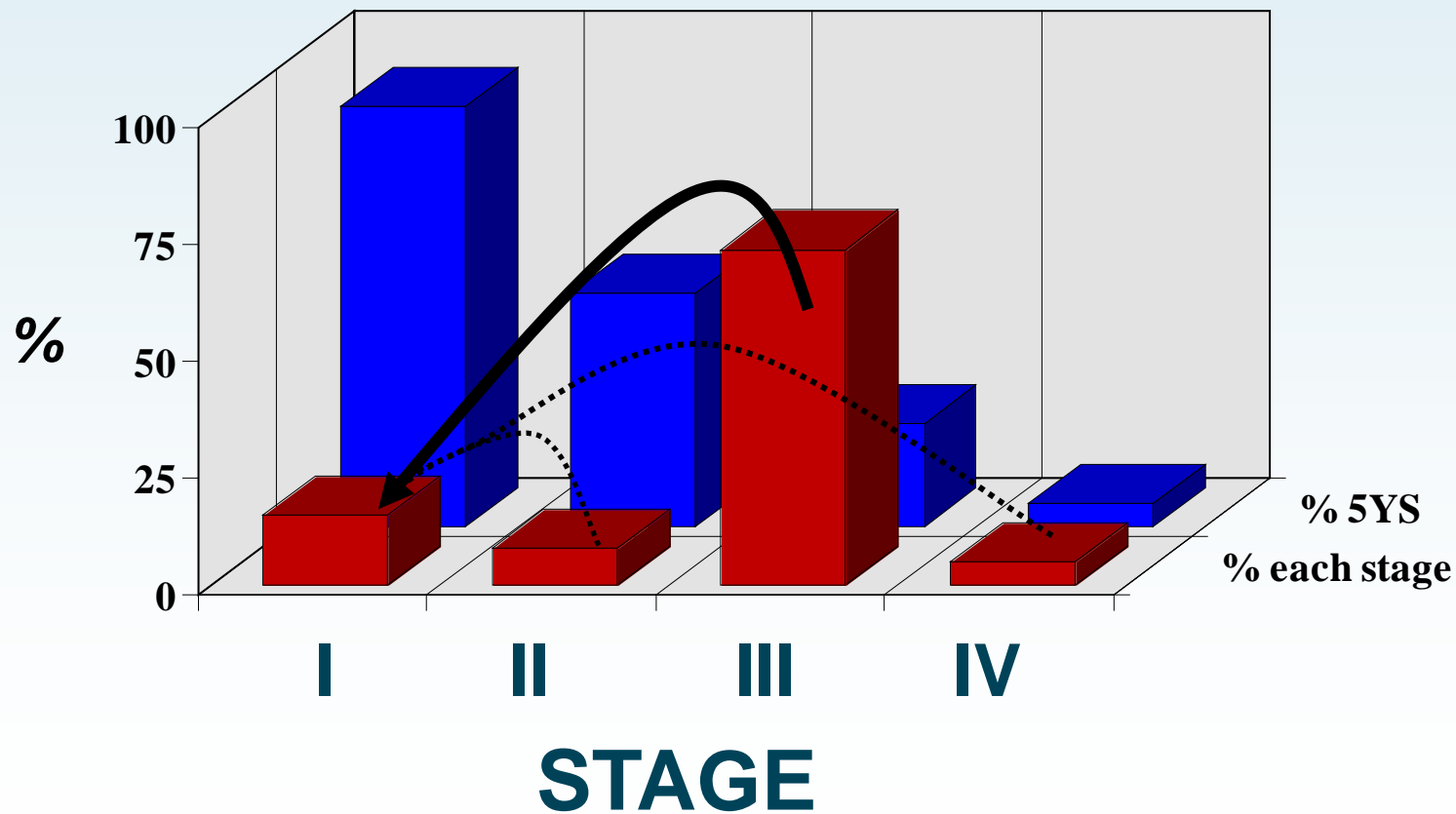
# Ovarian Cancer Screening

**International Cancer Screening Network**  
***Biennial Meeting, Oxford***  
***June 2010***

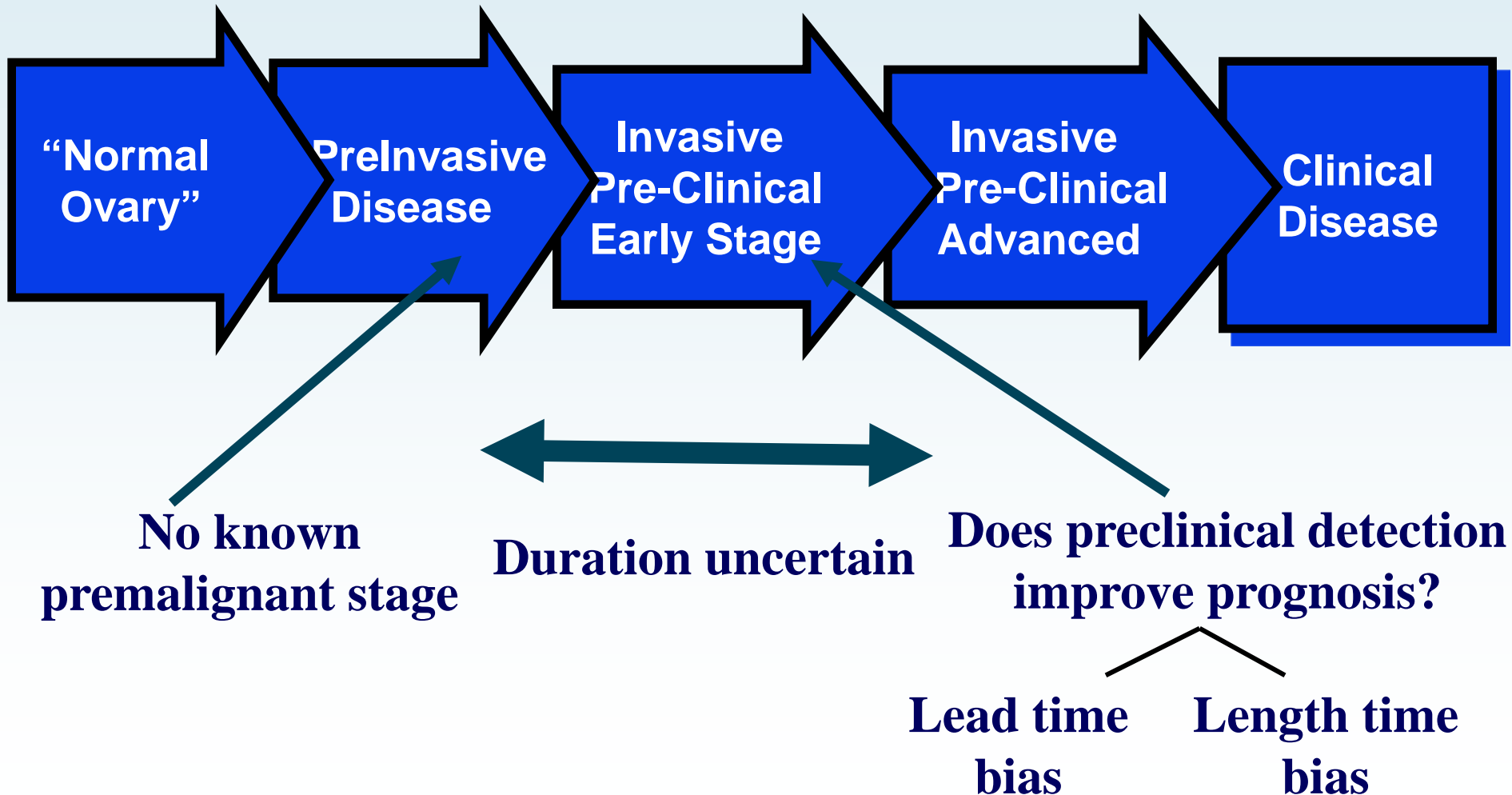
**Ian Jacobs**

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

## Rationale of Screening for Ovarian Cancer

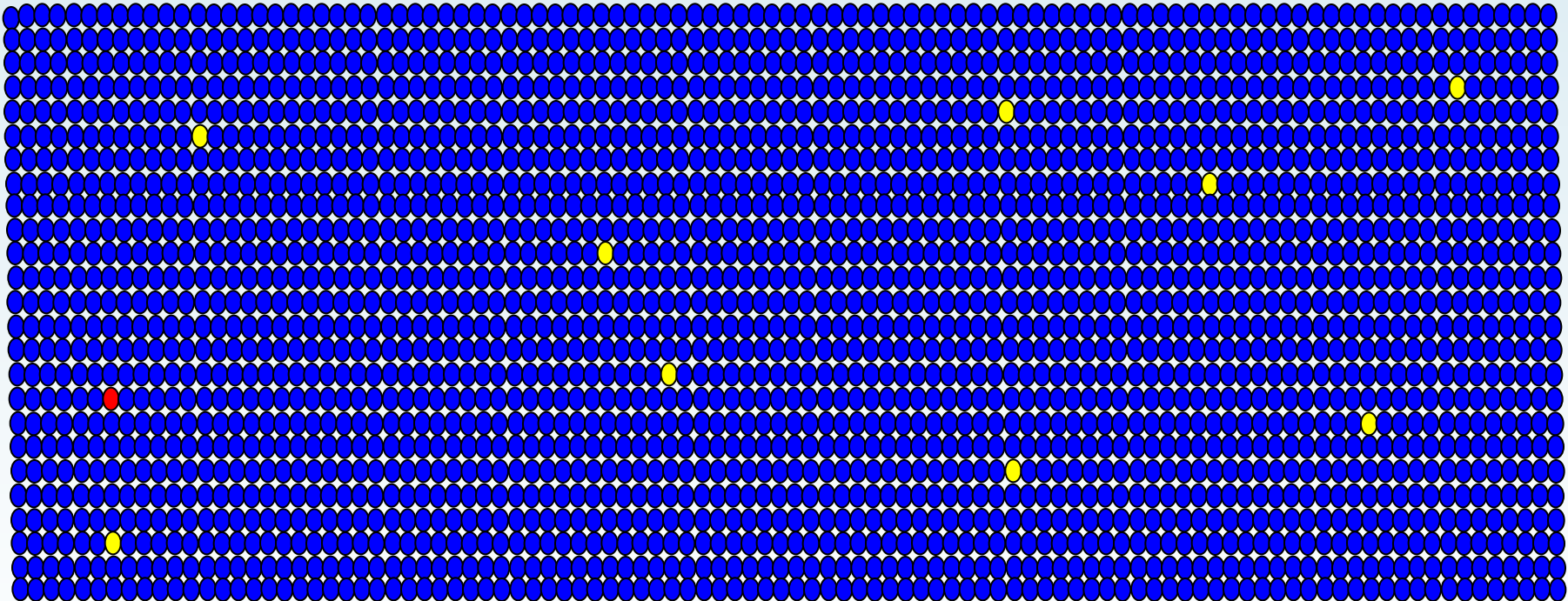


# Is the Natural History of Ovarian Cancer amenable to Screening ?



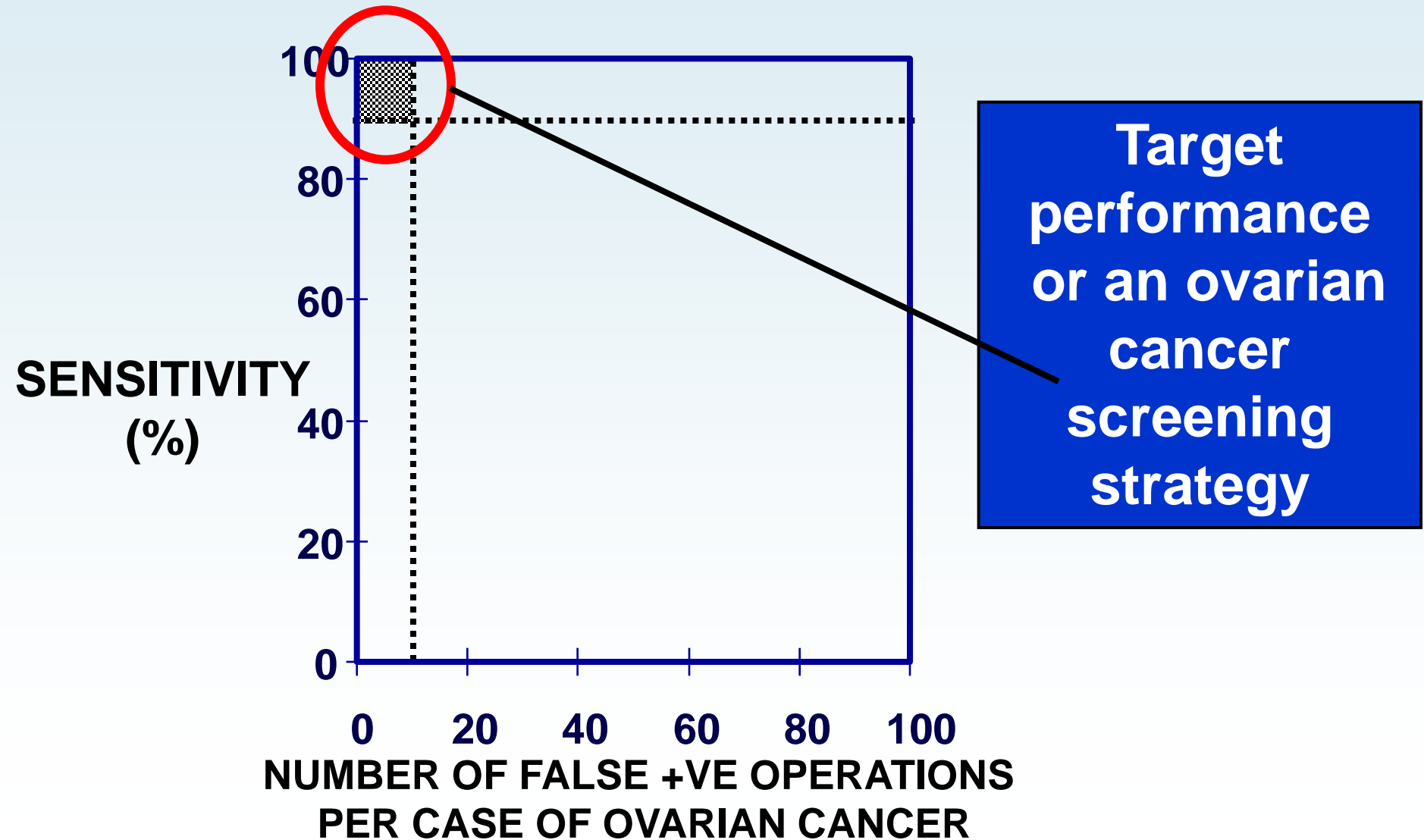
# The Challenge of Ovarian Cancer Screening

Incidence 1 in 2,500 pa in women >50y



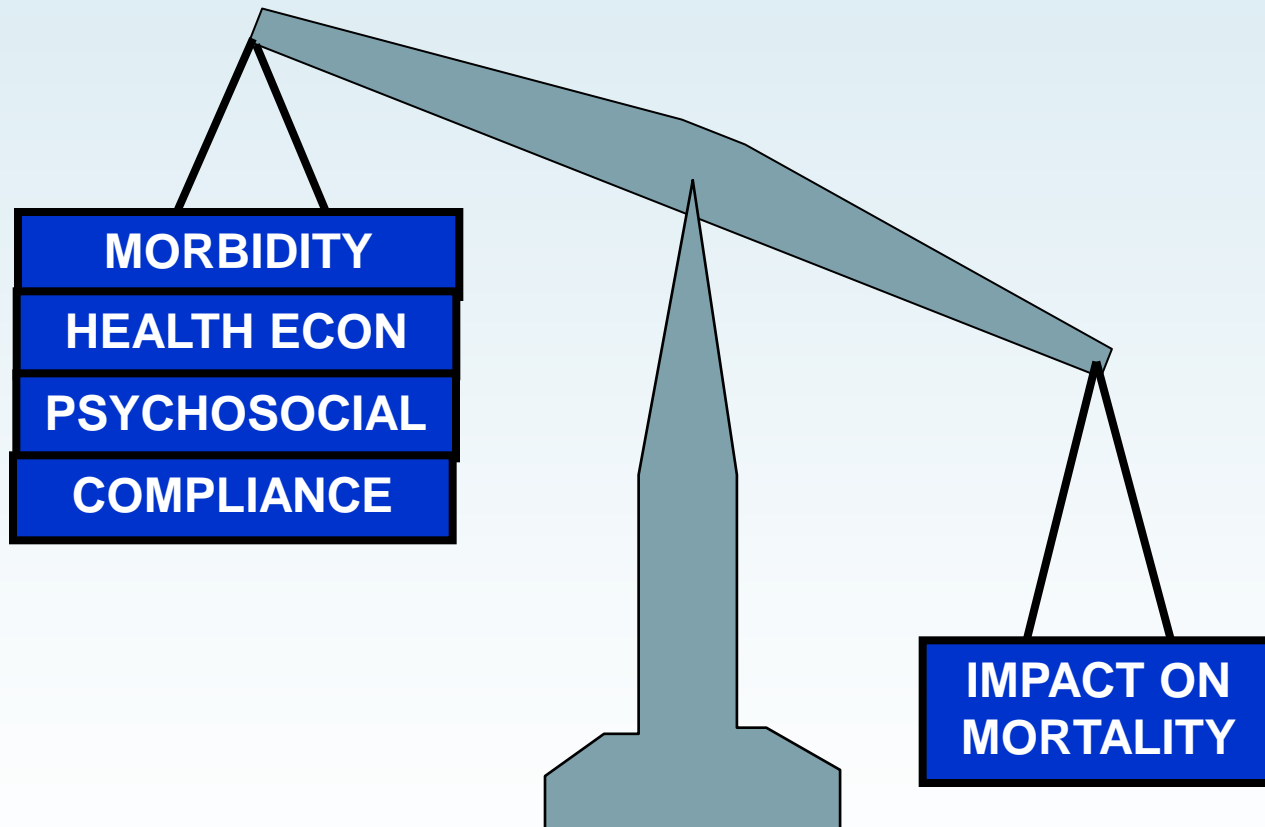
**Achieving a 10% PPV requires 99.6%  
specificity on general population screening**

# Achieving adequate Sensitivity & Specificity

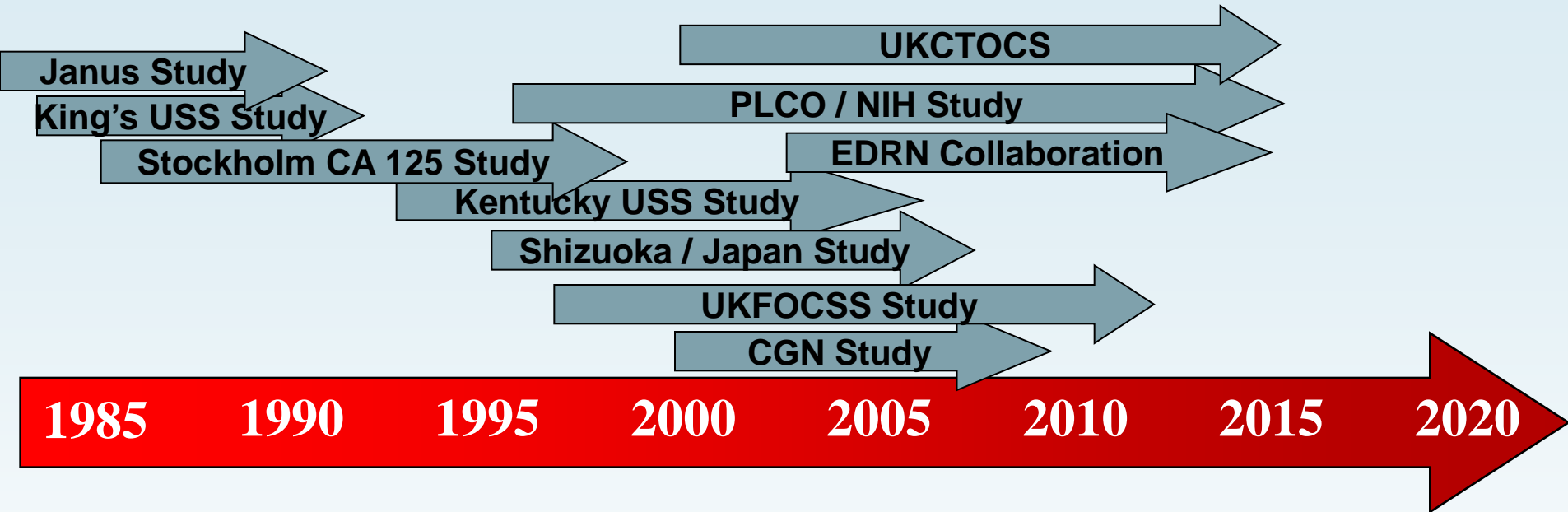


# Will Screening Decrease Mortality?

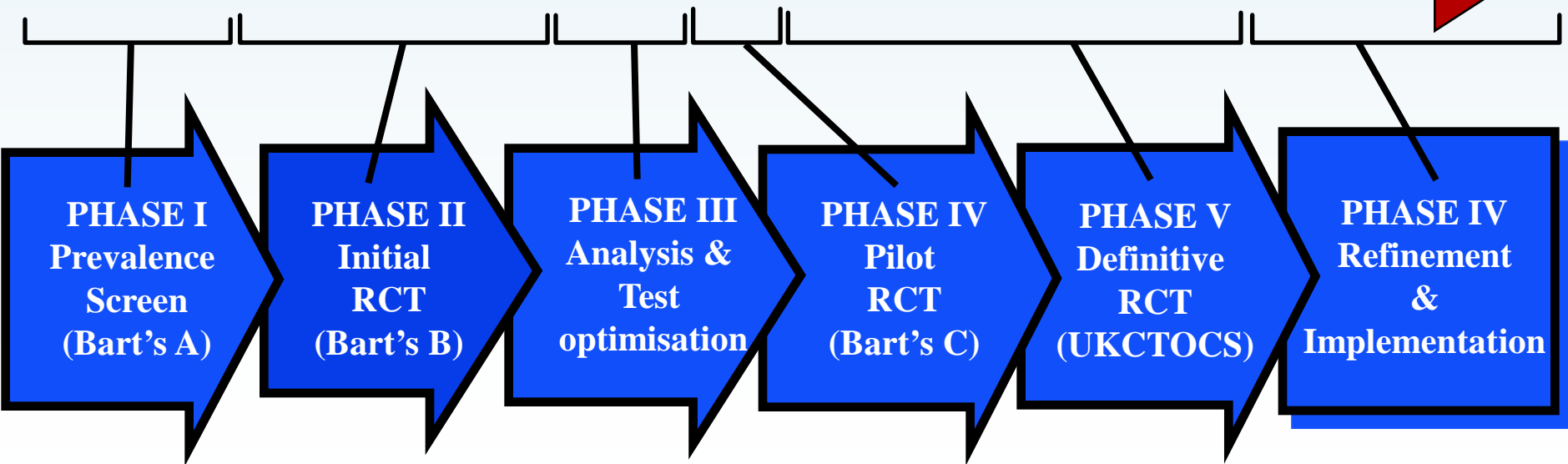
## Answer 2013/14



# OVARIAN CANCER SCREENING

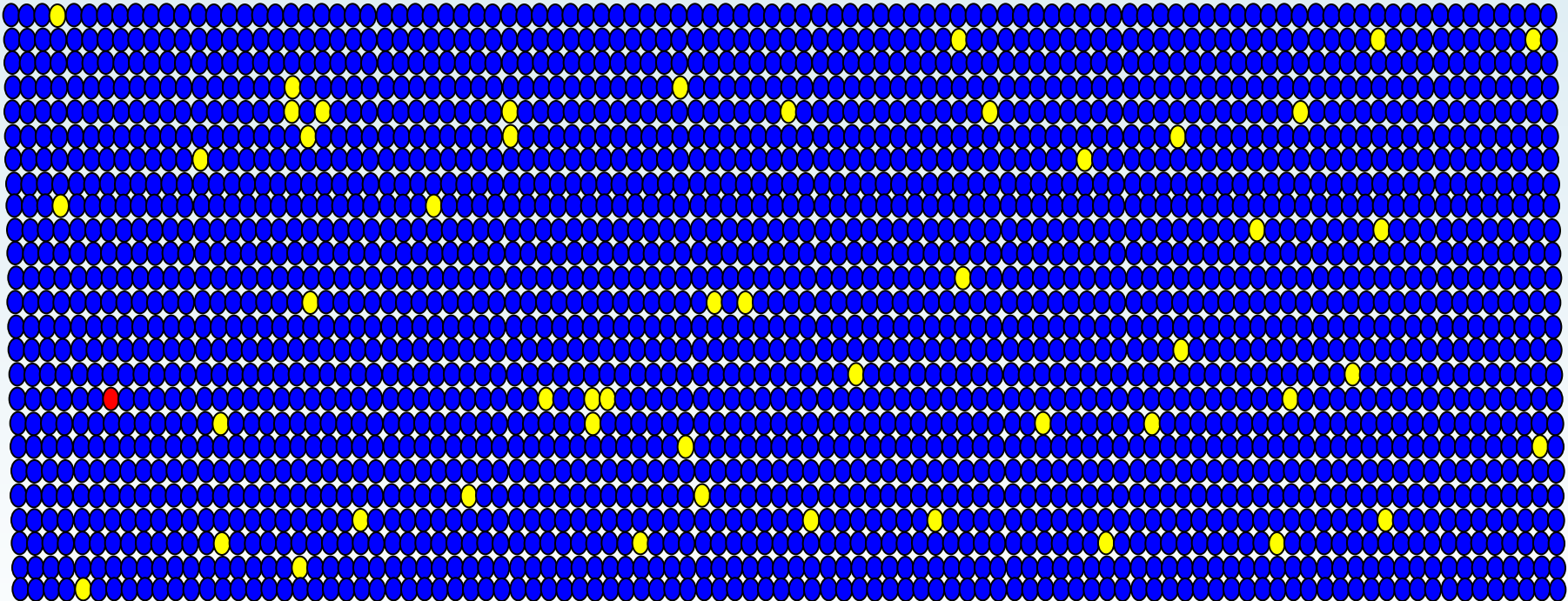


# OVARIAN CANCER SCREENING



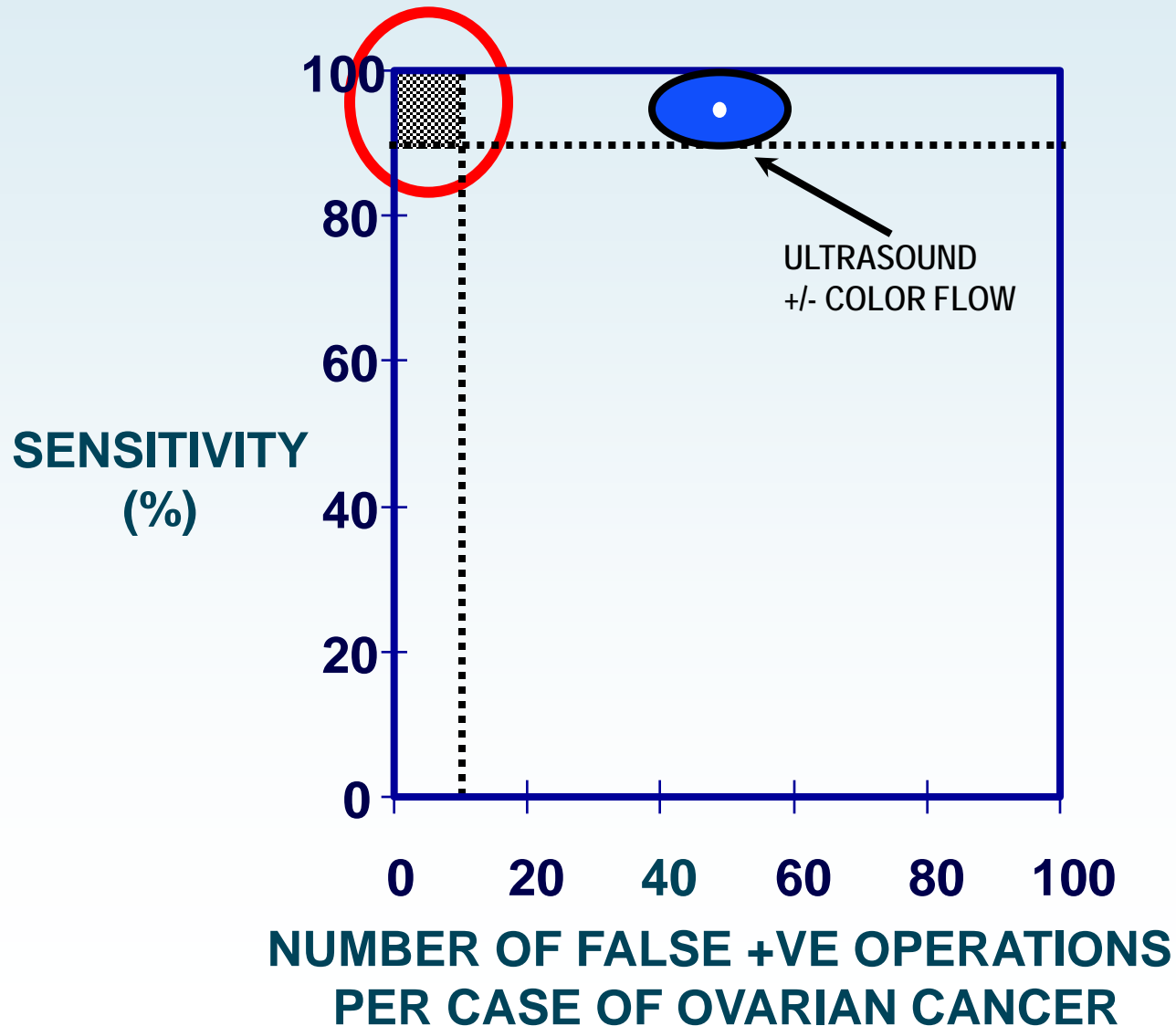


## Initial Ultrasound Studies



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

# Performance of Ultrasound Screening

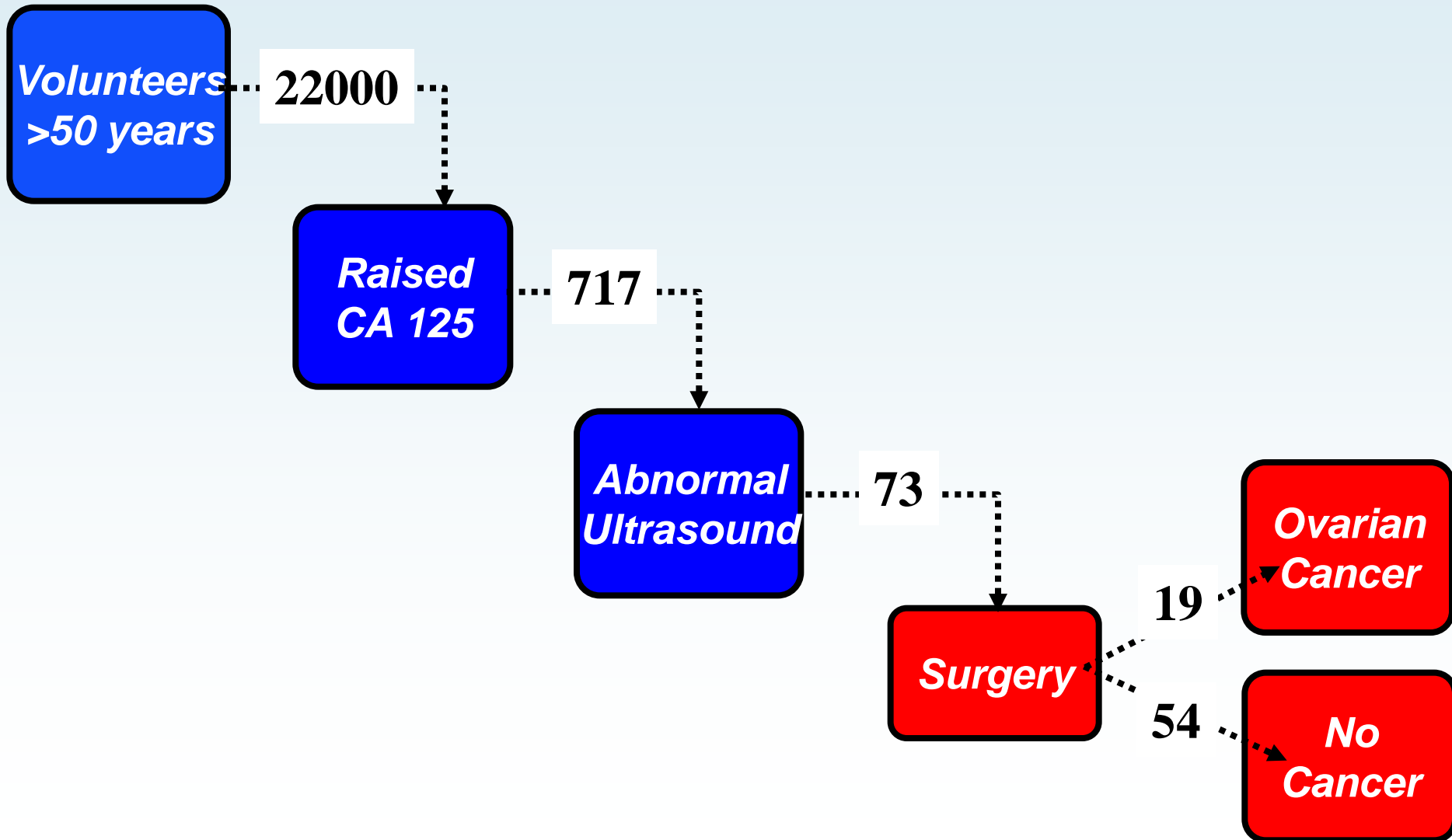




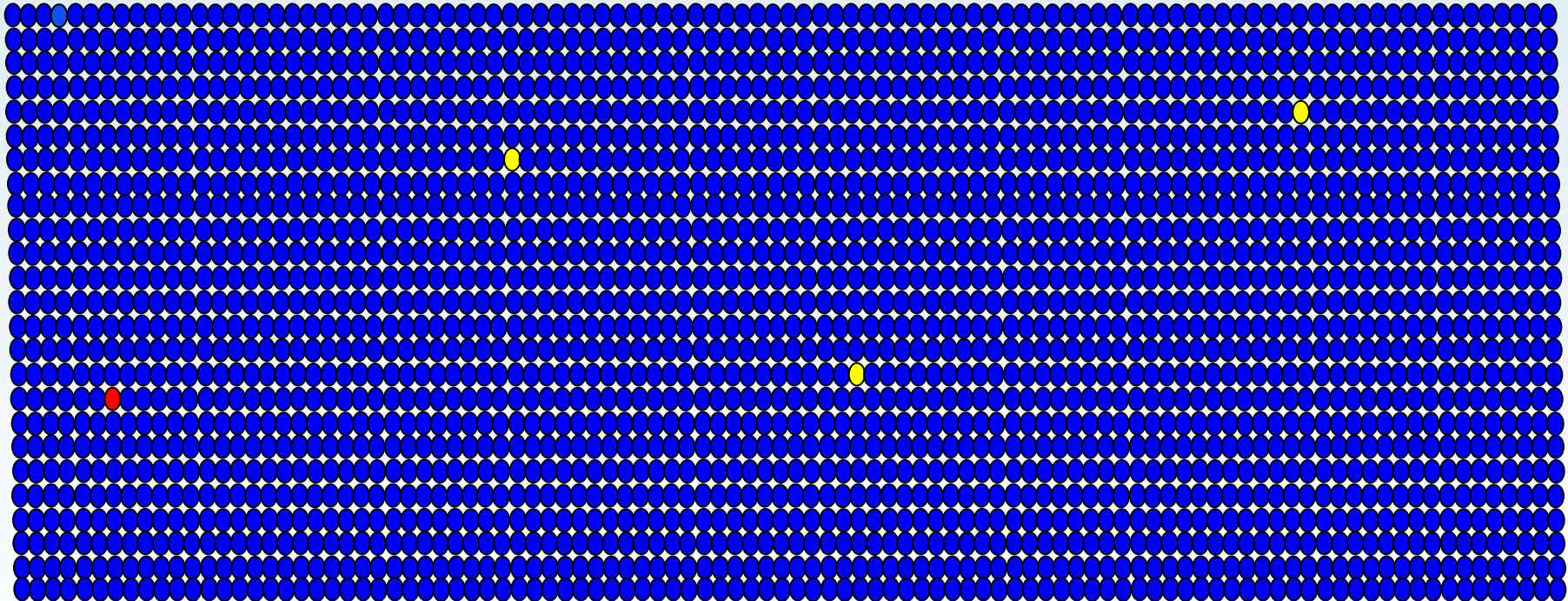
# Advantages of using a Tumour Marker for 1° Screen

- **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

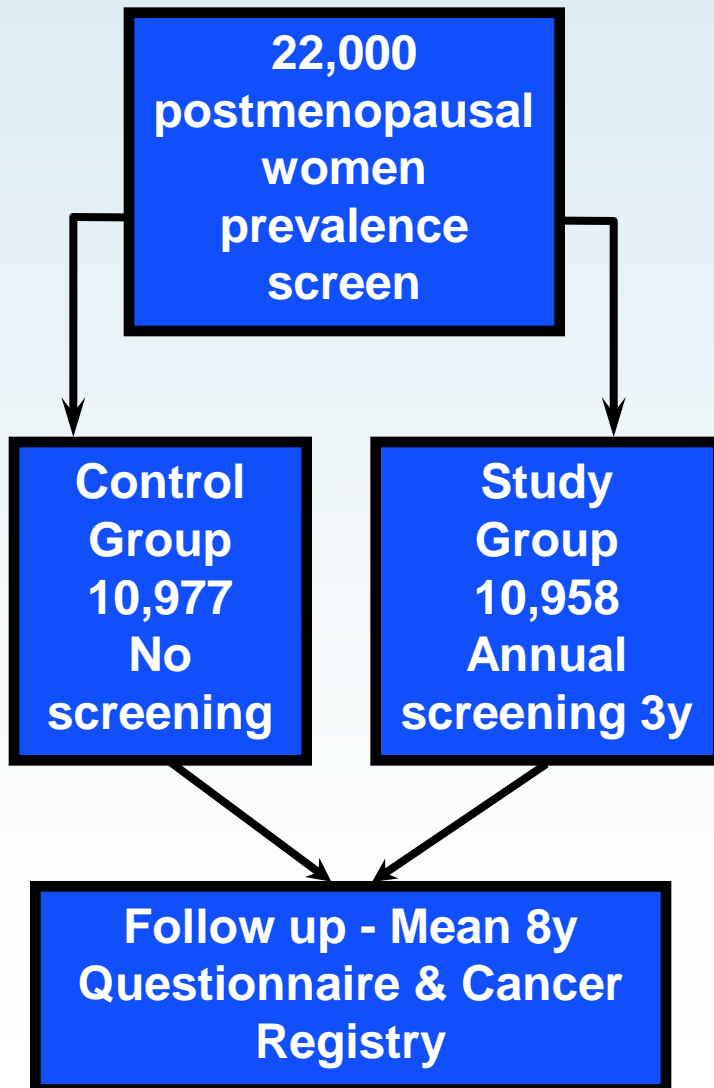


# Multimodal Screening has a low false positive rate



**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*

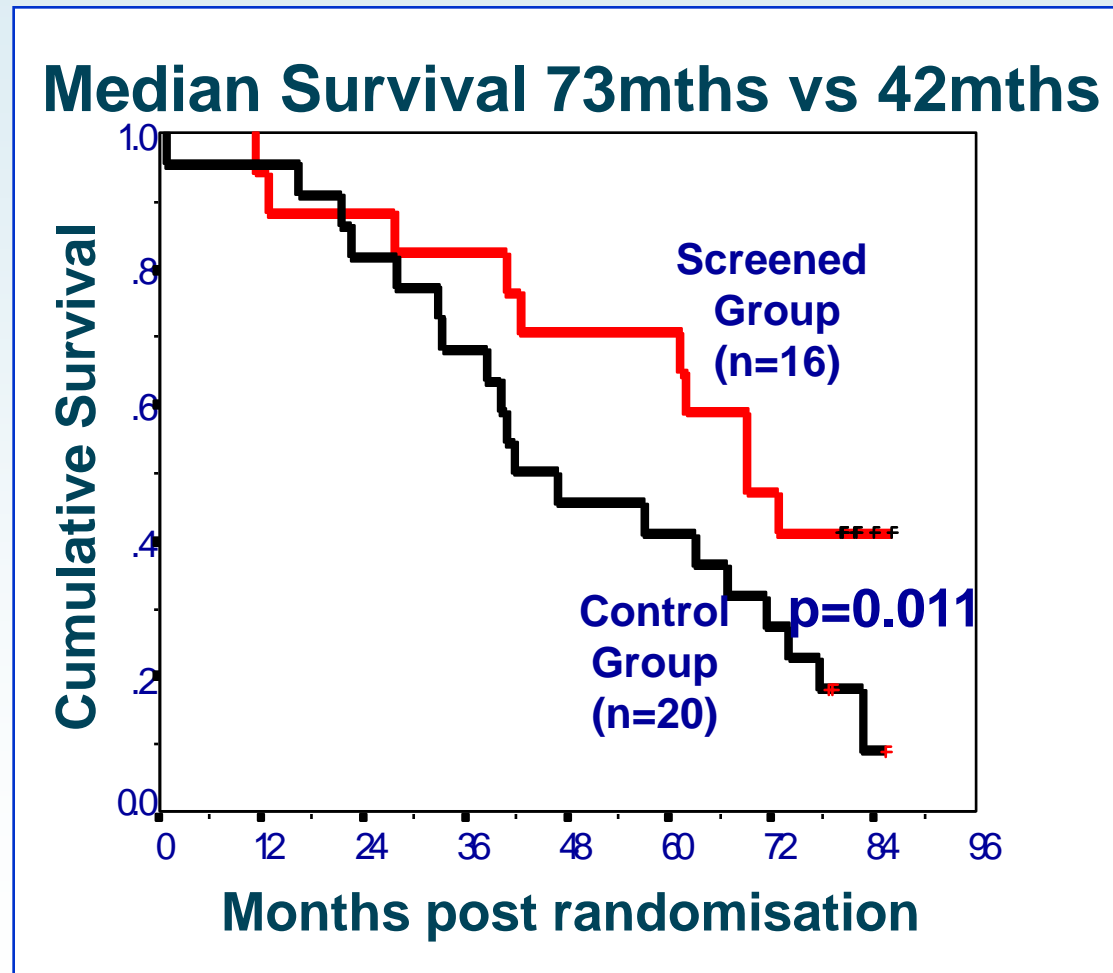
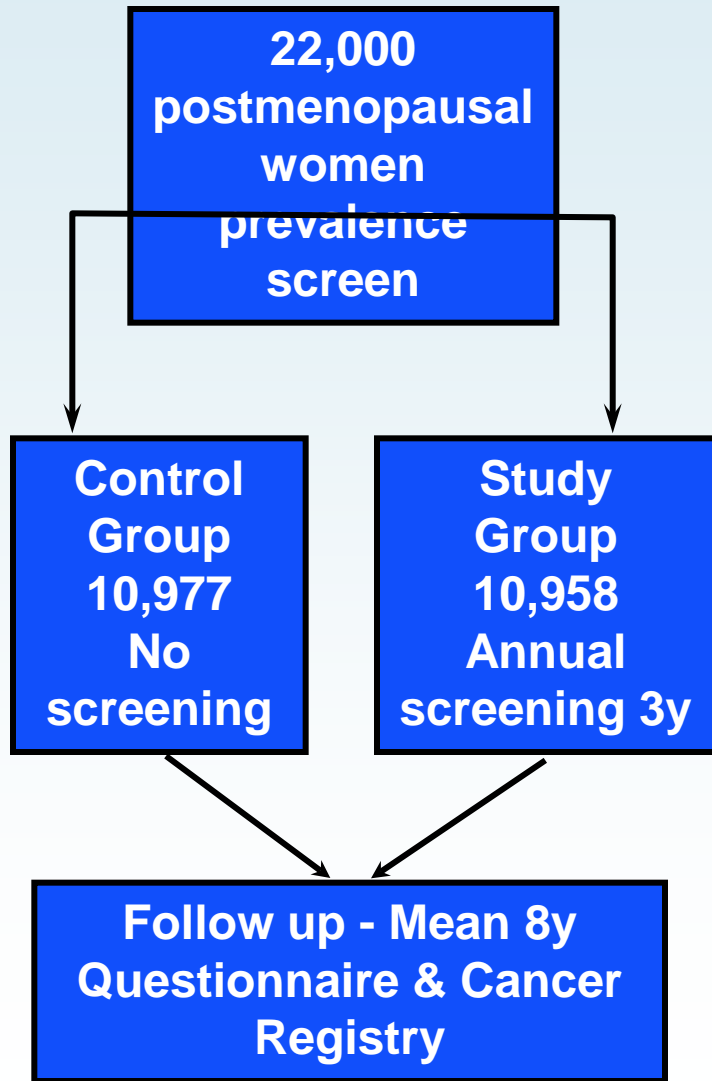
*OCP use*

*Family History*

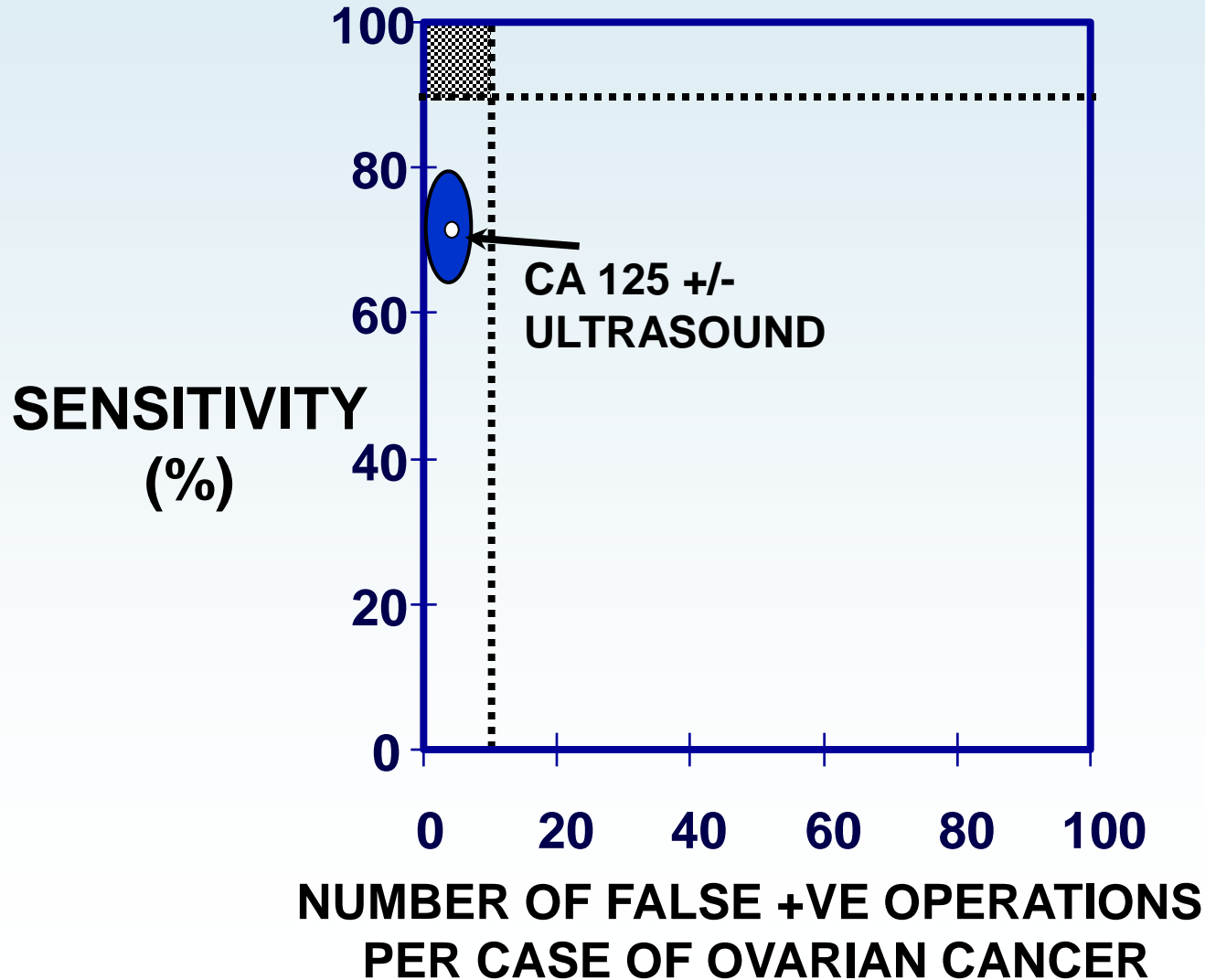
*Histological type of OC*

*Prevalence screen result*

## Improved Survival in Screen Arm

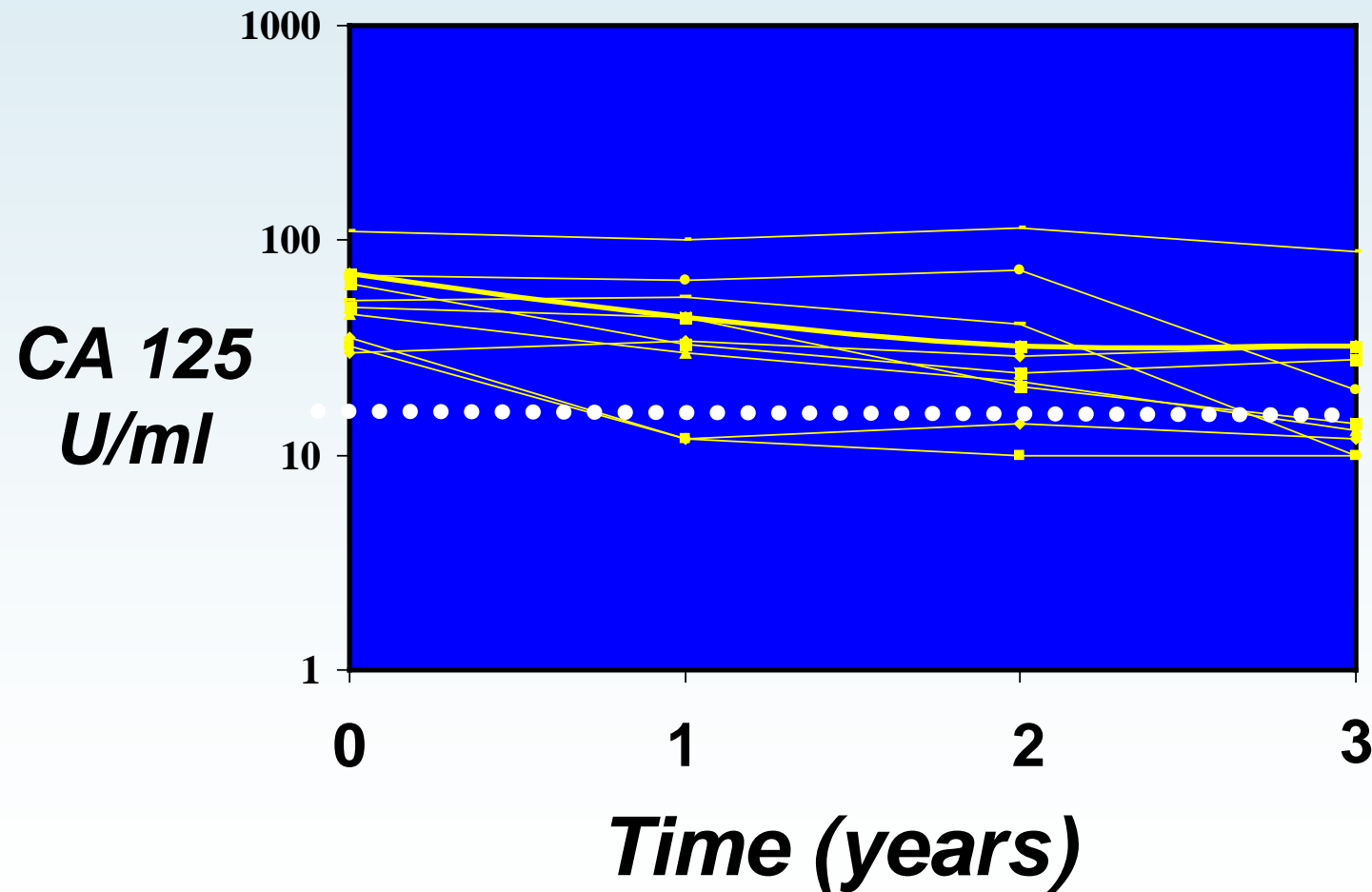


## Sensitivity of CA 125 only 67% at 1 year

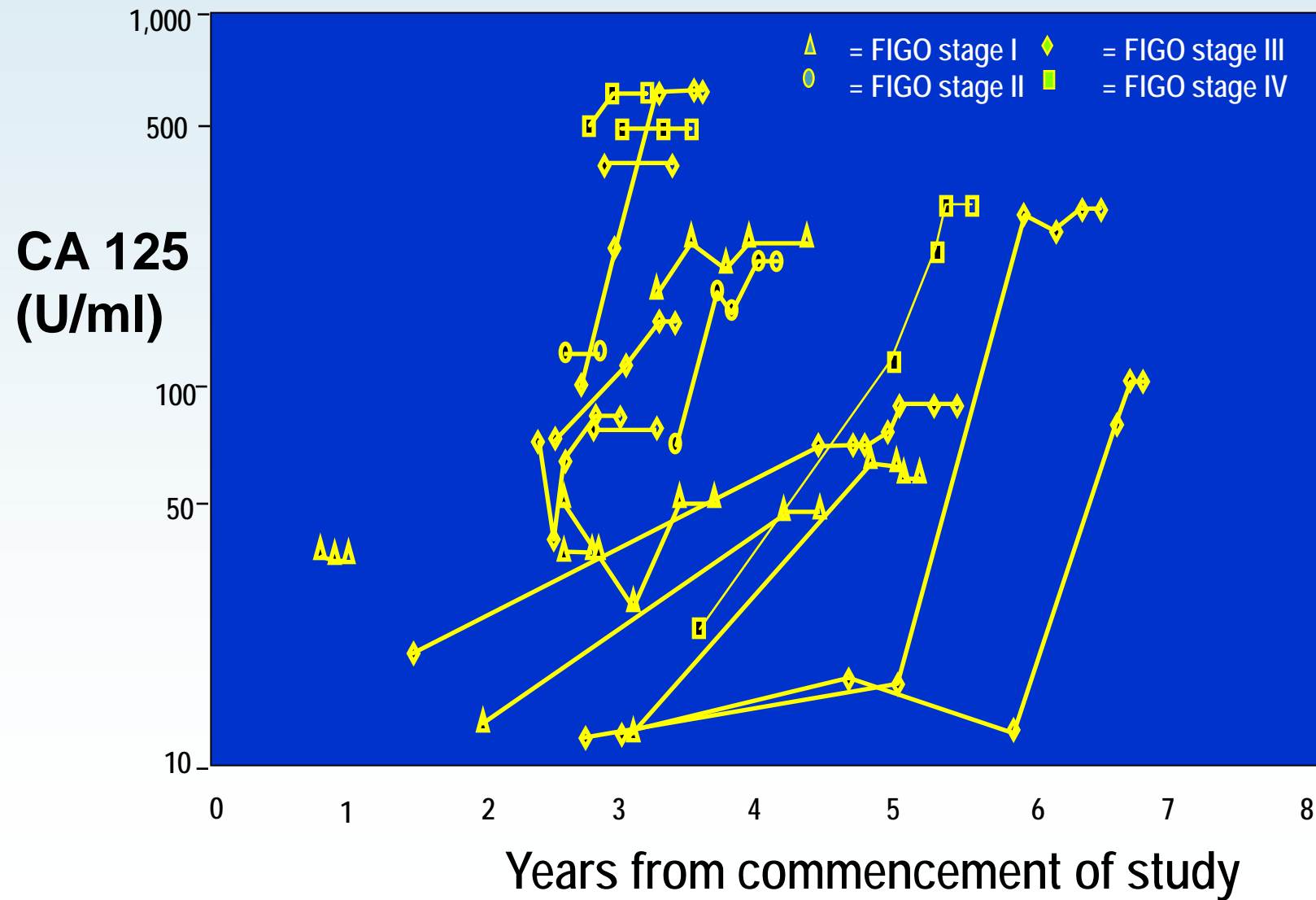




# CA 125 in asymptomatic women with CA 125 >30



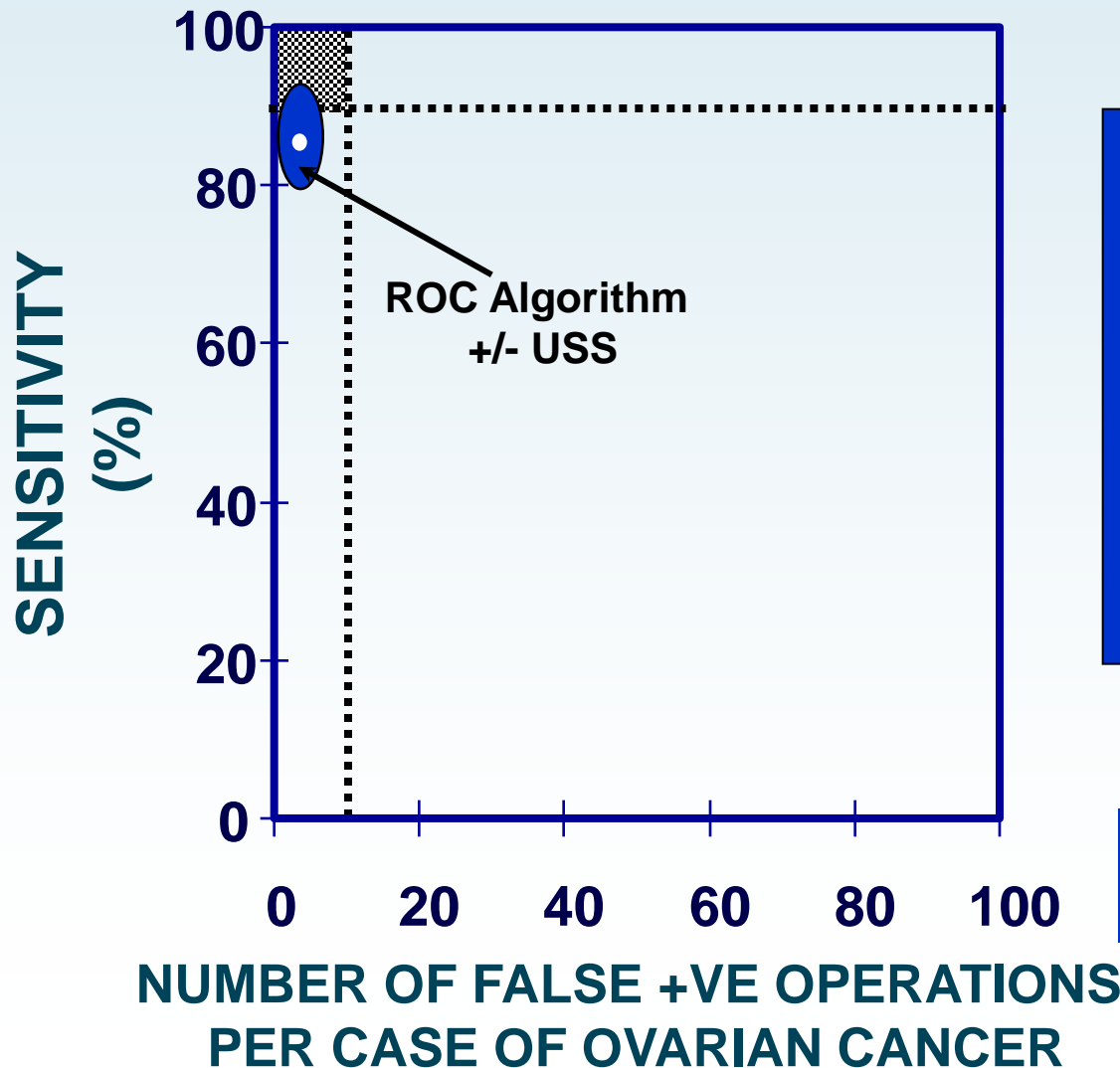
# CA 125 in asymptomatic women with OC



## 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



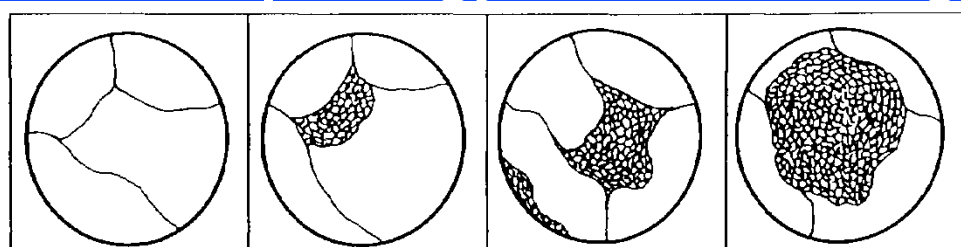
*Based on  
>50,000 screens  
Involving  
>30,000  
Women  
Stockholm +  
Bart's A/B*

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

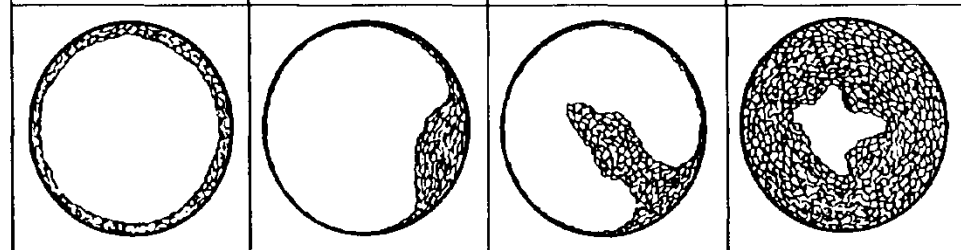
# Refinement of Ultrasound Screening strategy

- 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:

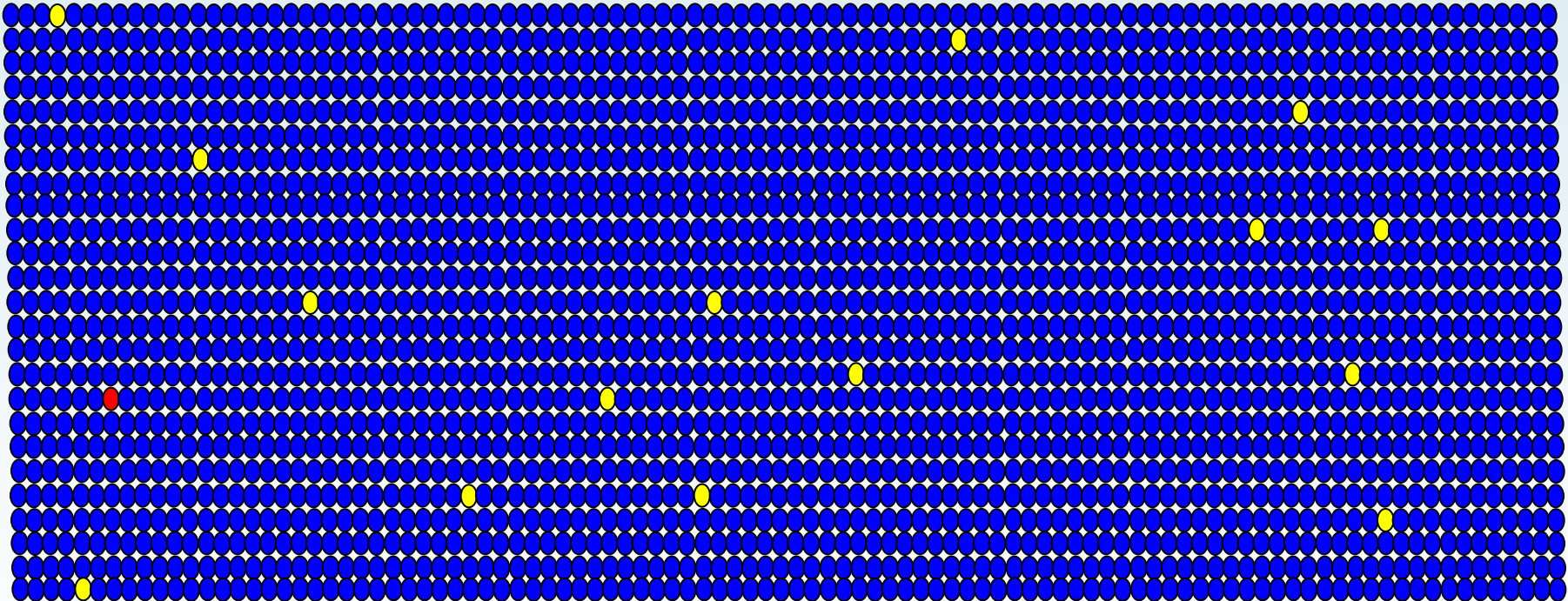
*Septa  
structure*



*Wall  
structure*

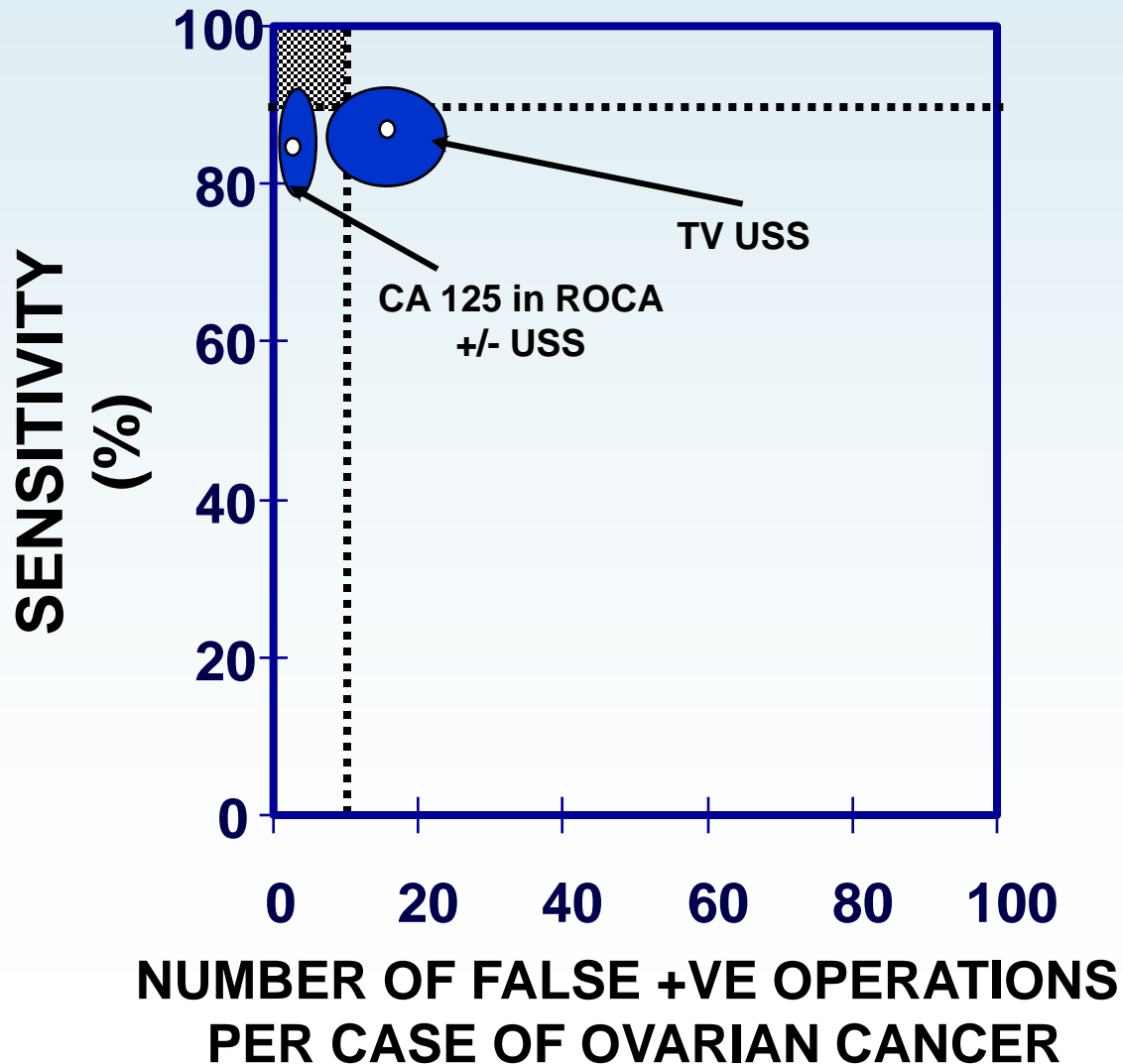


# Refining Ultrasound Screening

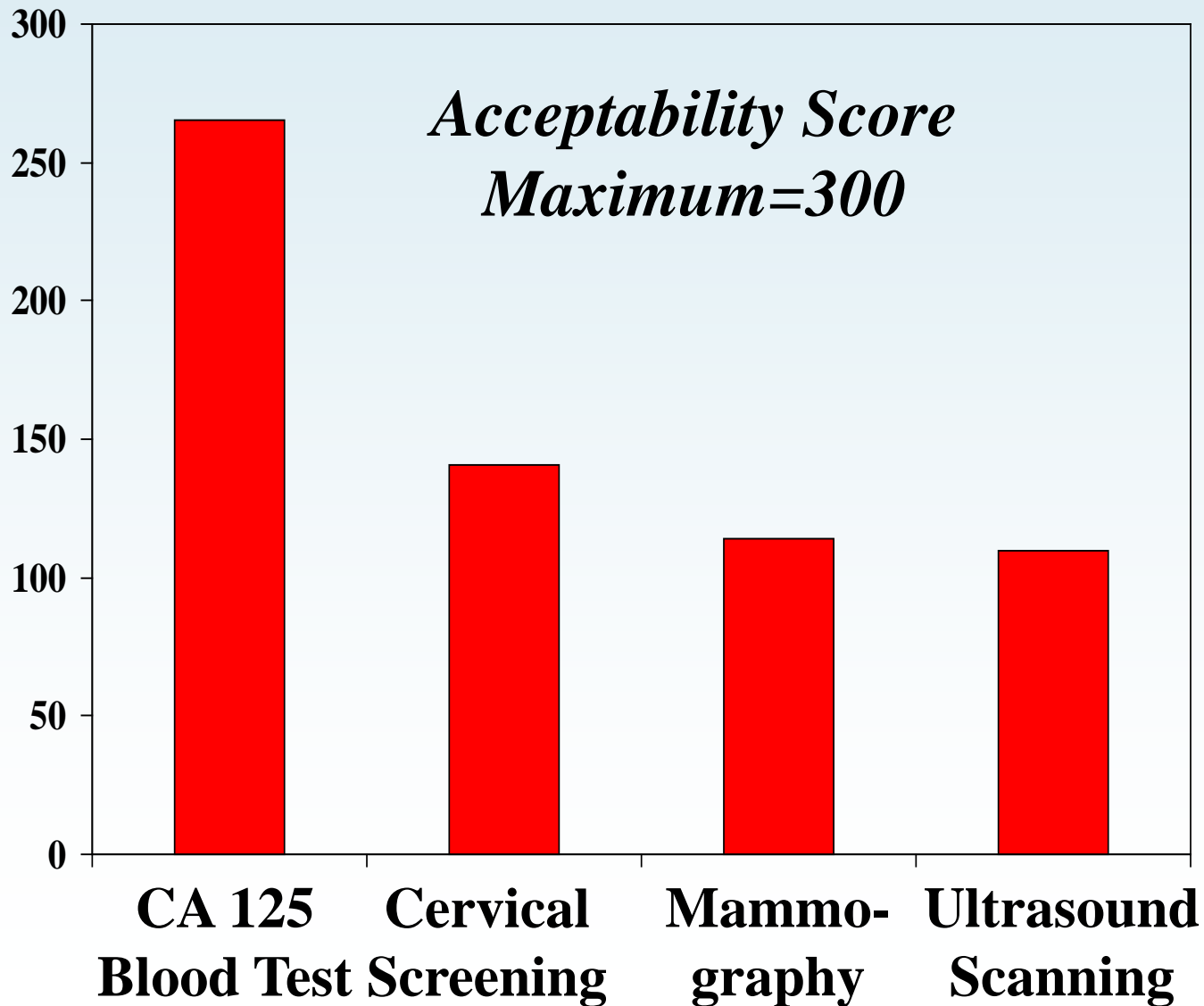


**7-20 unnecessary operations for  
each patient detected with ovarian cancer**

# Performance of Screening Strategies for OC



# Screening is Acceptable to Women in the UK

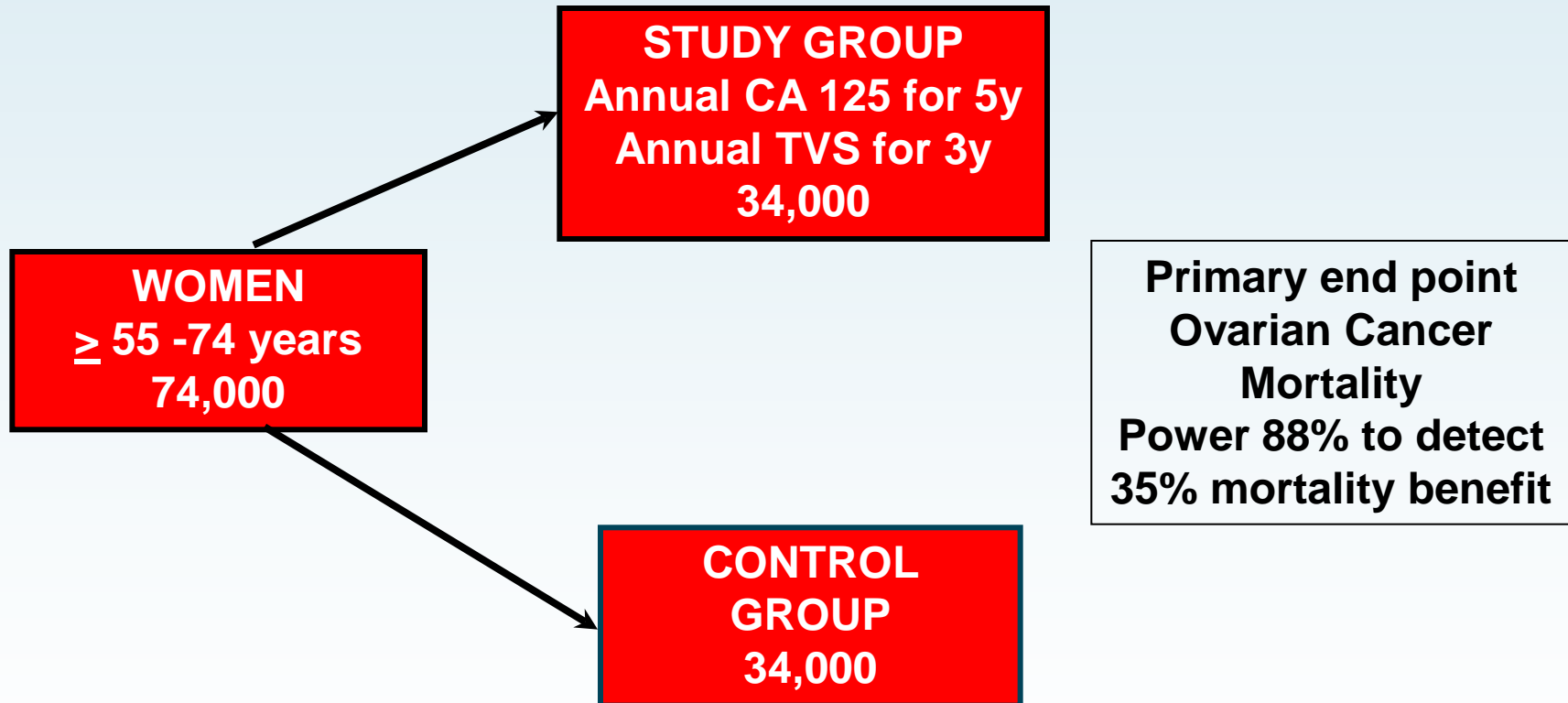




# STATUS OF POPULATION SCREENING FOR OVARIAN CANCER

Feasible & Acceptable ✓	High Specificity ✓
Satisfactory PPV ✓	Reasonable Sensitivity ✓
Improved Survival <b>Probably</b>	Reduced mortality <b>Possibly</b>

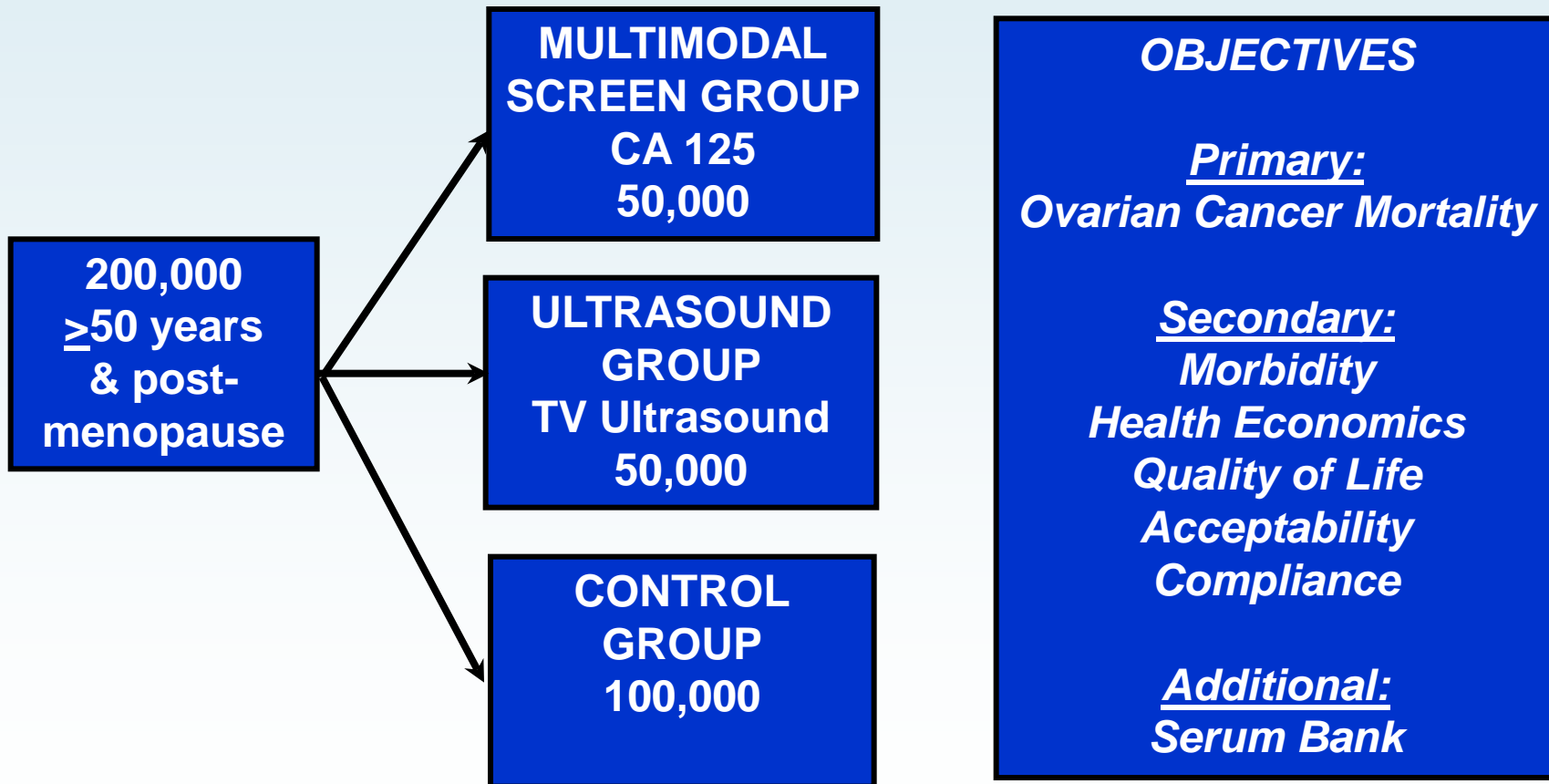
# NIH PLCO (Prostate, Lung, Colorectal & Ovarian) Cancer Screening Trial



All women followed up for 13 years by postal questionnaire

# UKCTOCS

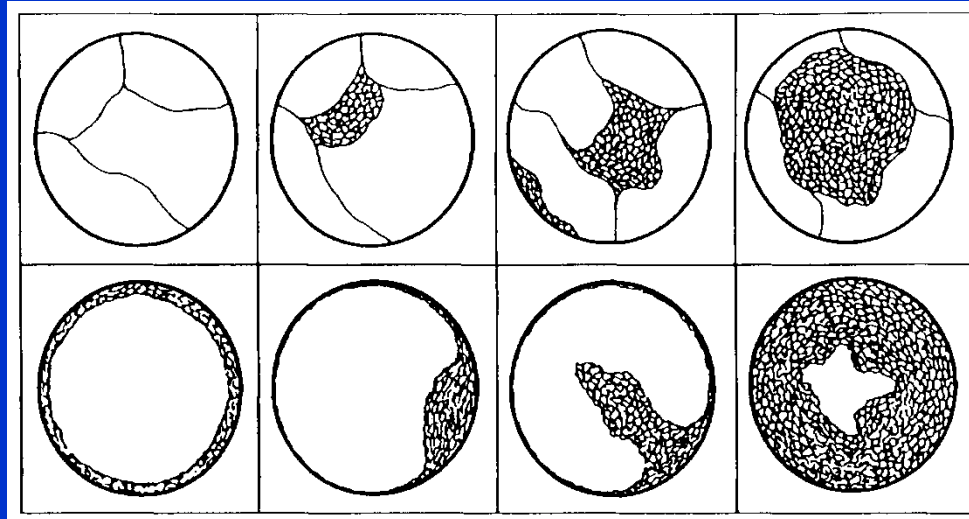
## UK Collaborative Trial of Ovarian Cancer Screening



## METHODS: USS Protocol

- Transvaginal Scanning
- Morphology based scoring systems:

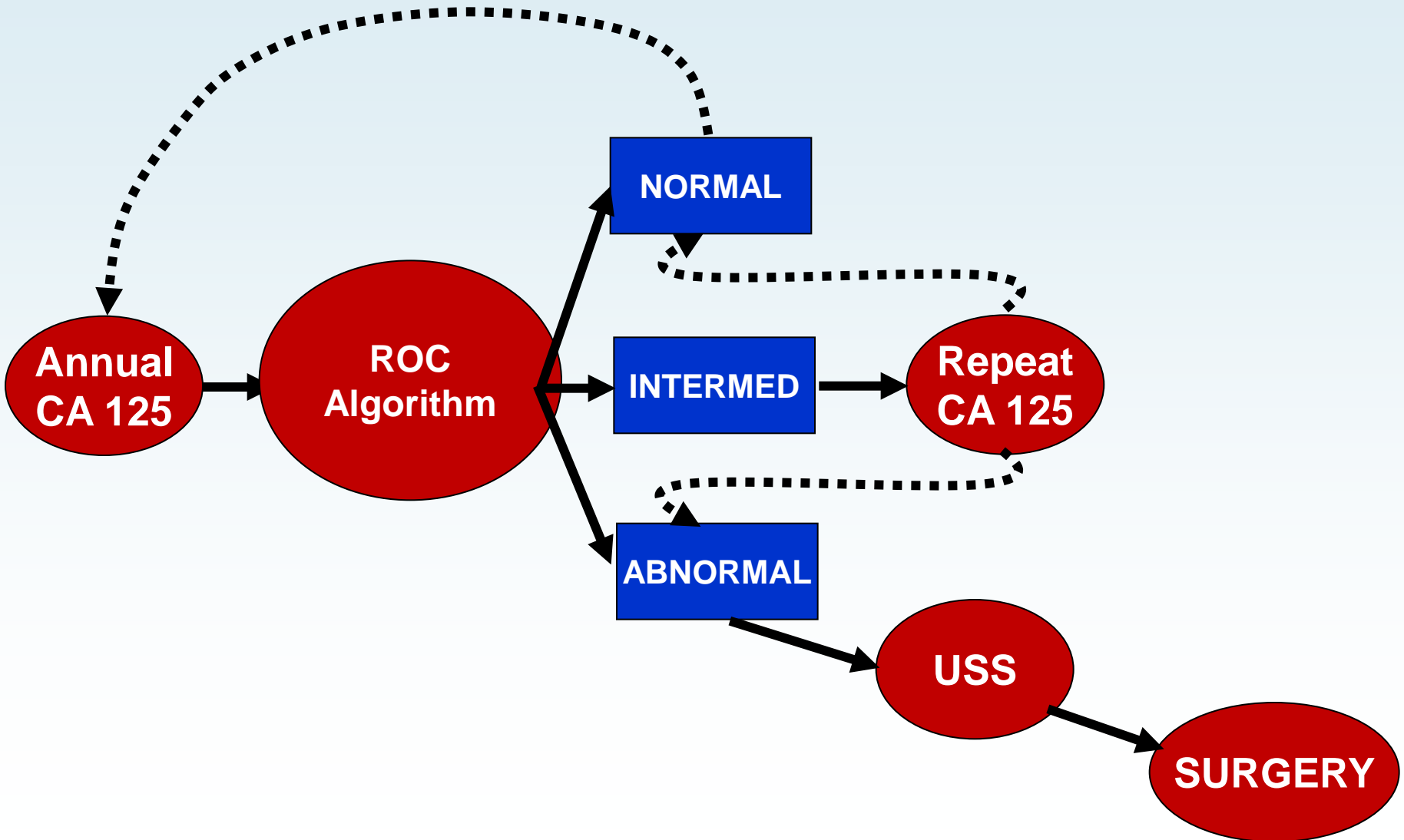
*Septa  
structure*



*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**

# METHODS: Logistics

- 13 Centres
- 50 permanent staff and 9
- 27 Primary Care Trusts
- 250 General Practitioners
- 200,000 consents
- 300,000 ultrasound screens
- 500,000 CA 125 tests + b
- 600,000 results letters
- 1.2 million invitations

Volunteer Ref	Name	Date and Time	Type	Status	Minor Type
10070032	Mrs. MARY DOBSON	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10067576	Mrs. SANDRA JOAN YOHN	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10070181	Ms. EVELYN H E PROCTOR	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10070555	Mrs. LINDA A APPLEBY	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10068791	Mrs. ELIZABETH CAMILLA ANDREWS	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10072302	Mrs. MARY MAY	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10069427	Mrs. MAVIS JENNER	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10068784	Ms. GILLIAN E GALBRAITH	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10072375	Mrs. ROSE MUSTARD	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt
10070297	Mrs. GILLIAN WENDY MALT	8th Sep 2003 09:15	Initial recruitment appointment and blood sample	Appointment not yet due	Initial appt

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

## Co-Investigators

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

## ACKNOWLEDGEMENTS



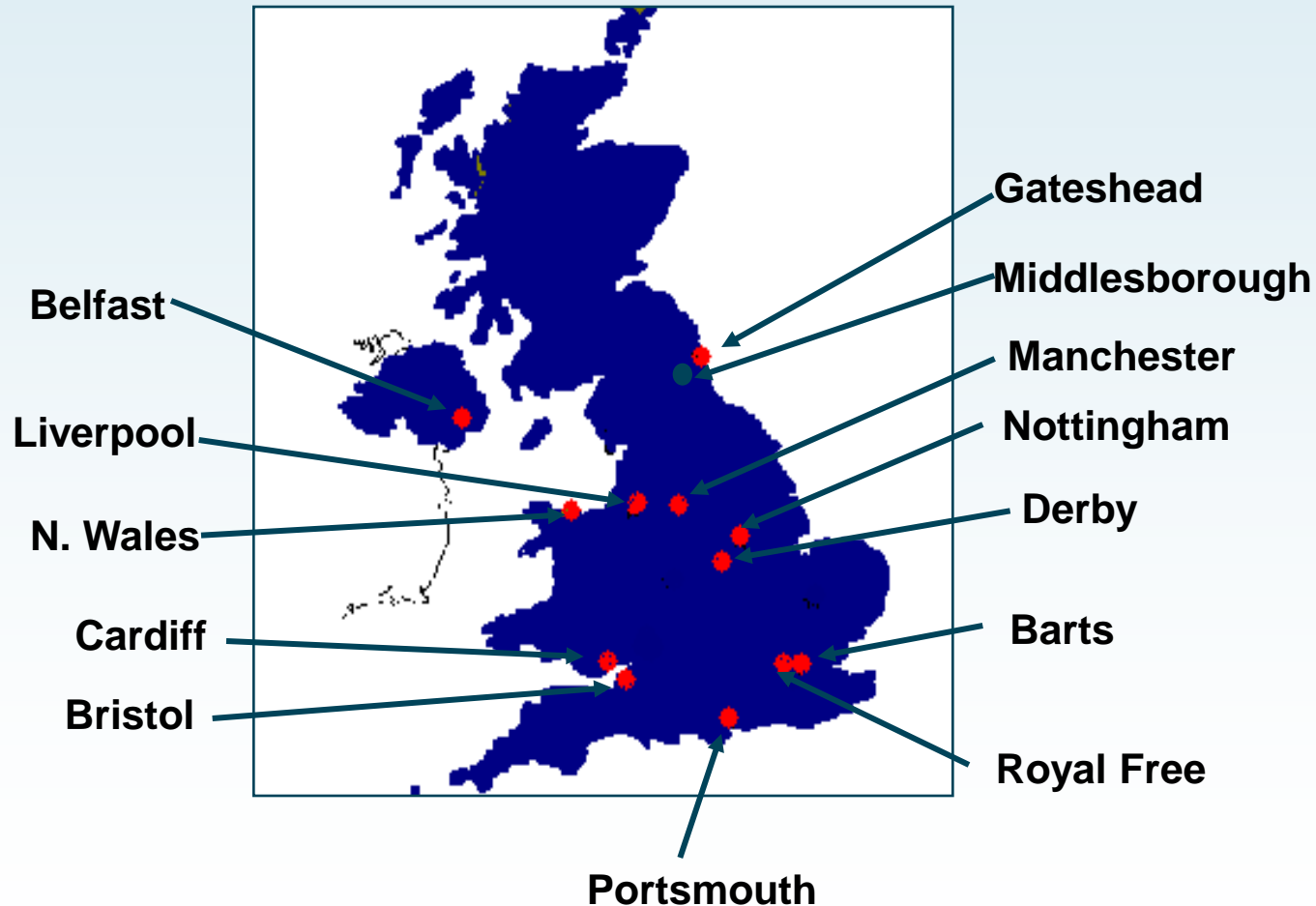
## UKCTOCS + UKFOCSS

### 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)

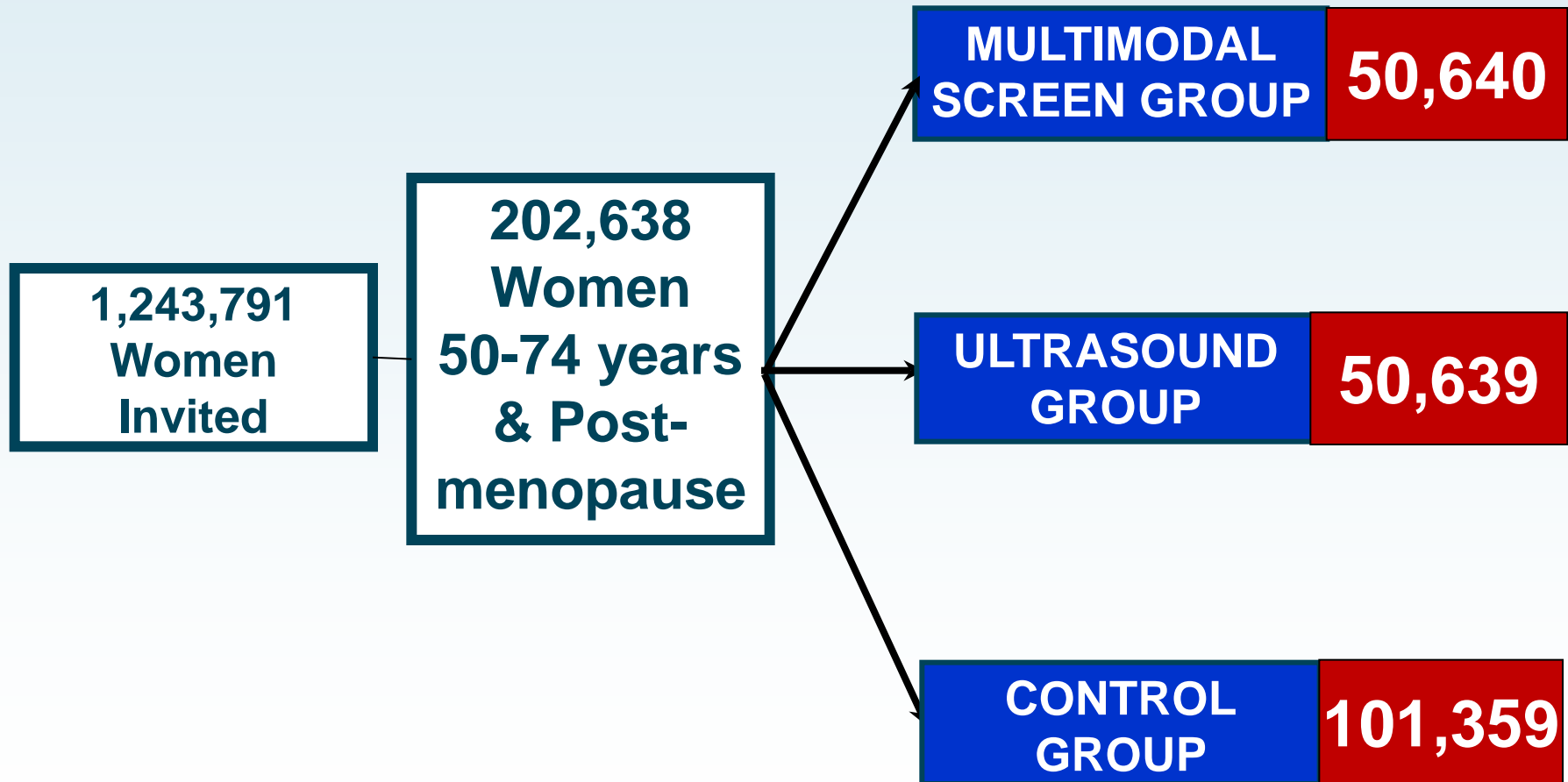
## UKFOCSS Collaborators

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)

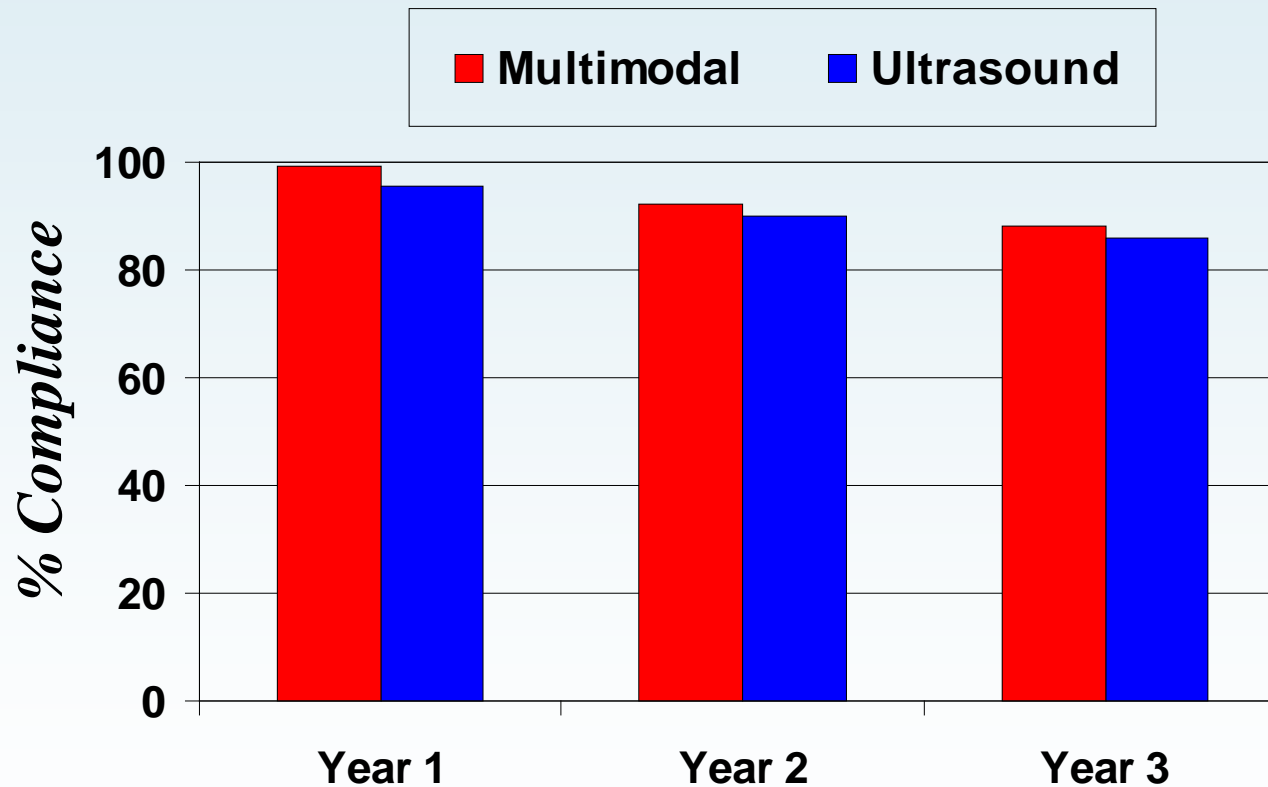
## International Collaborators

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

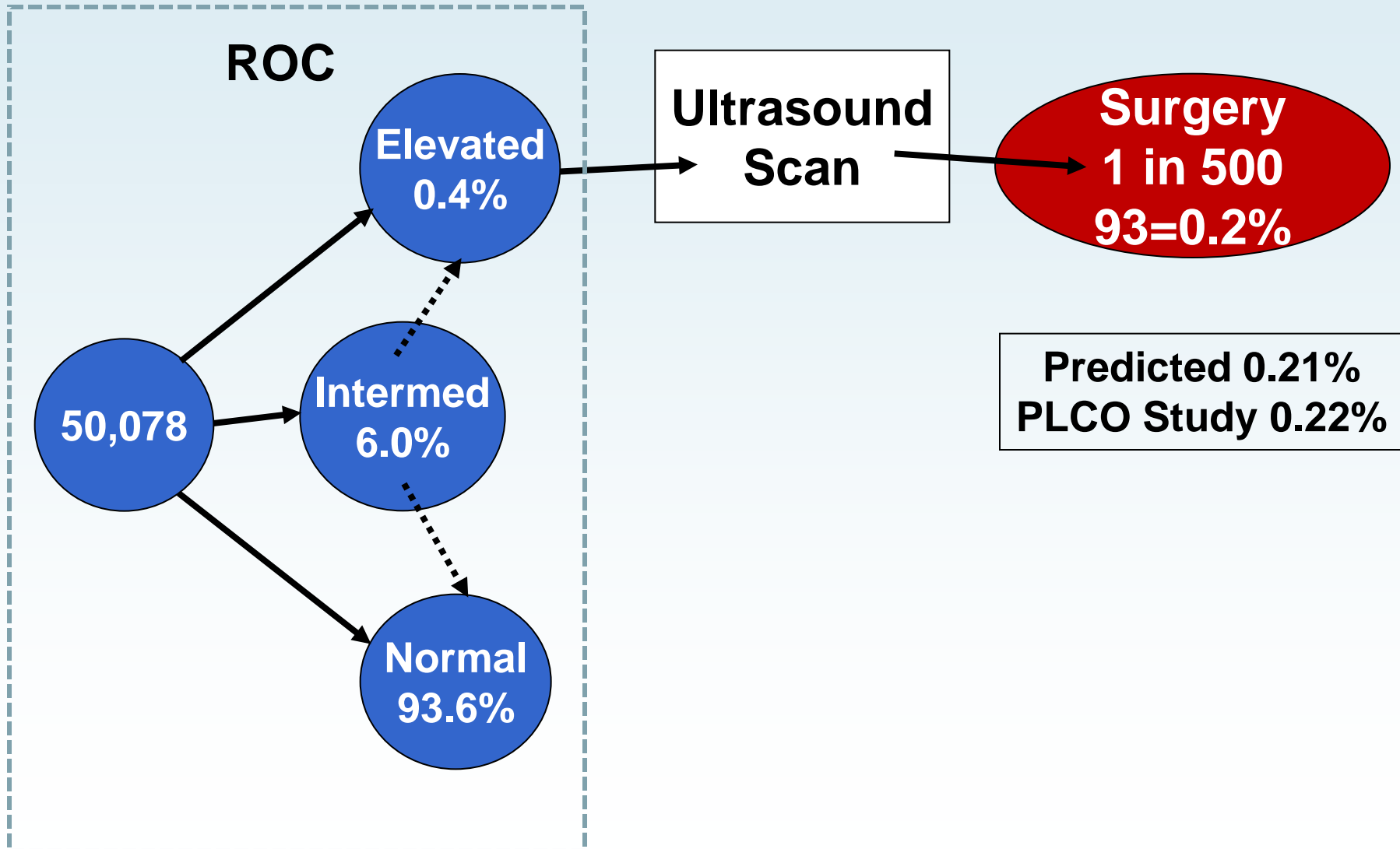
## UKCTOCS: Randomisation



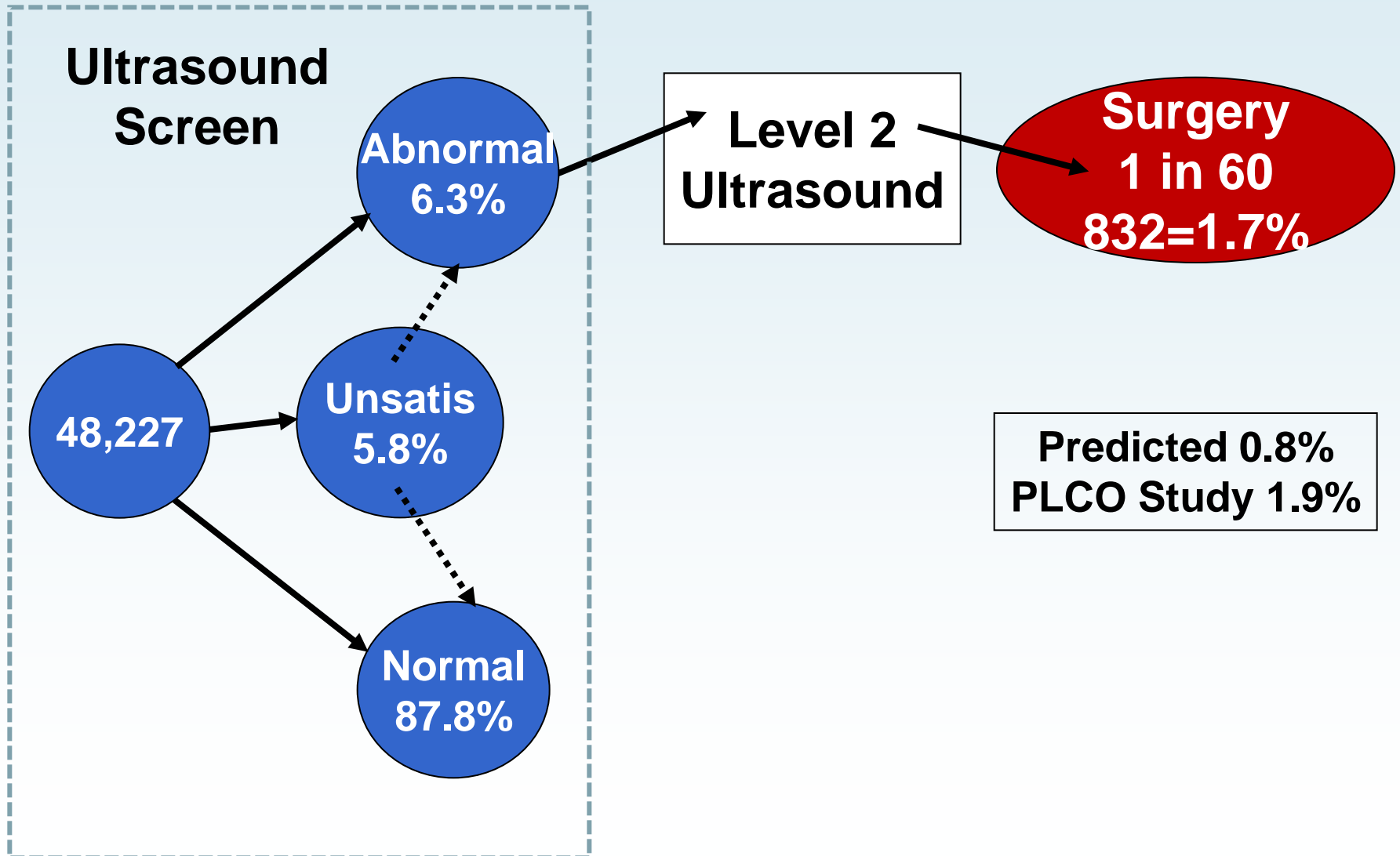
# UKCTOCS: Screening Compliance



# UKCTOCS: Multimodal Screening



# UKCTOCS: Ultrasound Screening





# UKCTOCS: Pathology in Screen Positives

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

## UKCTOCS: Test Sensitivity

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



## UKCTOCS: Test Sensitivity

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

# UKCTOCS: Stage distribution of Screen detected cancers

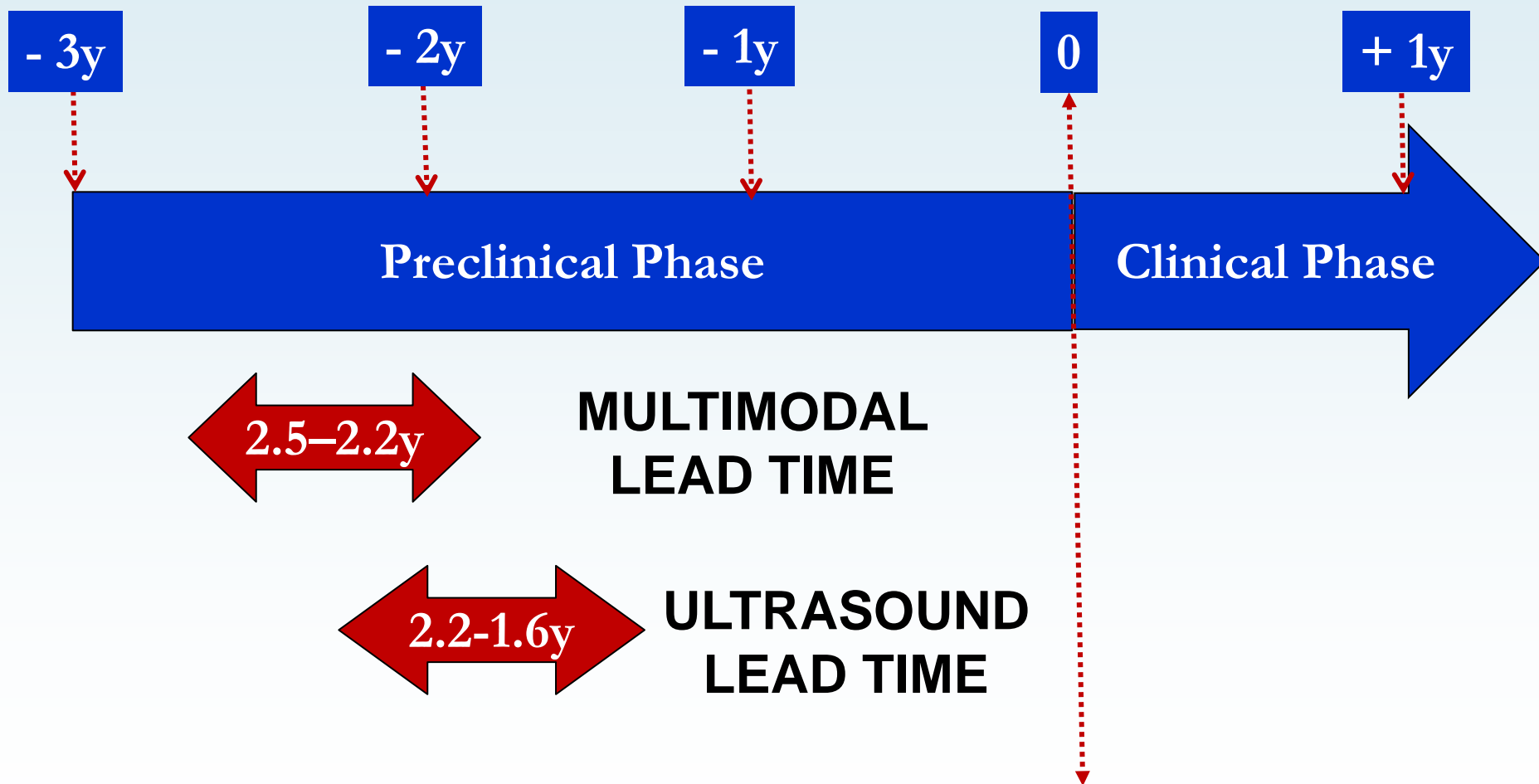
Stage	M	U
I	14	9
II	2	2
III	16	10
IV	0	1
Not staged	1	1
<b>Early stage (I/II) %</b>	<b>48.50%</b>	<b>47.80%</b>

**PLCO**

**15%**

**28%**

## UKCTOCS: Estimating Lead Time



Acceptable False  
Positive Rate? ✓

Feasibility +  
Compliance? ✓

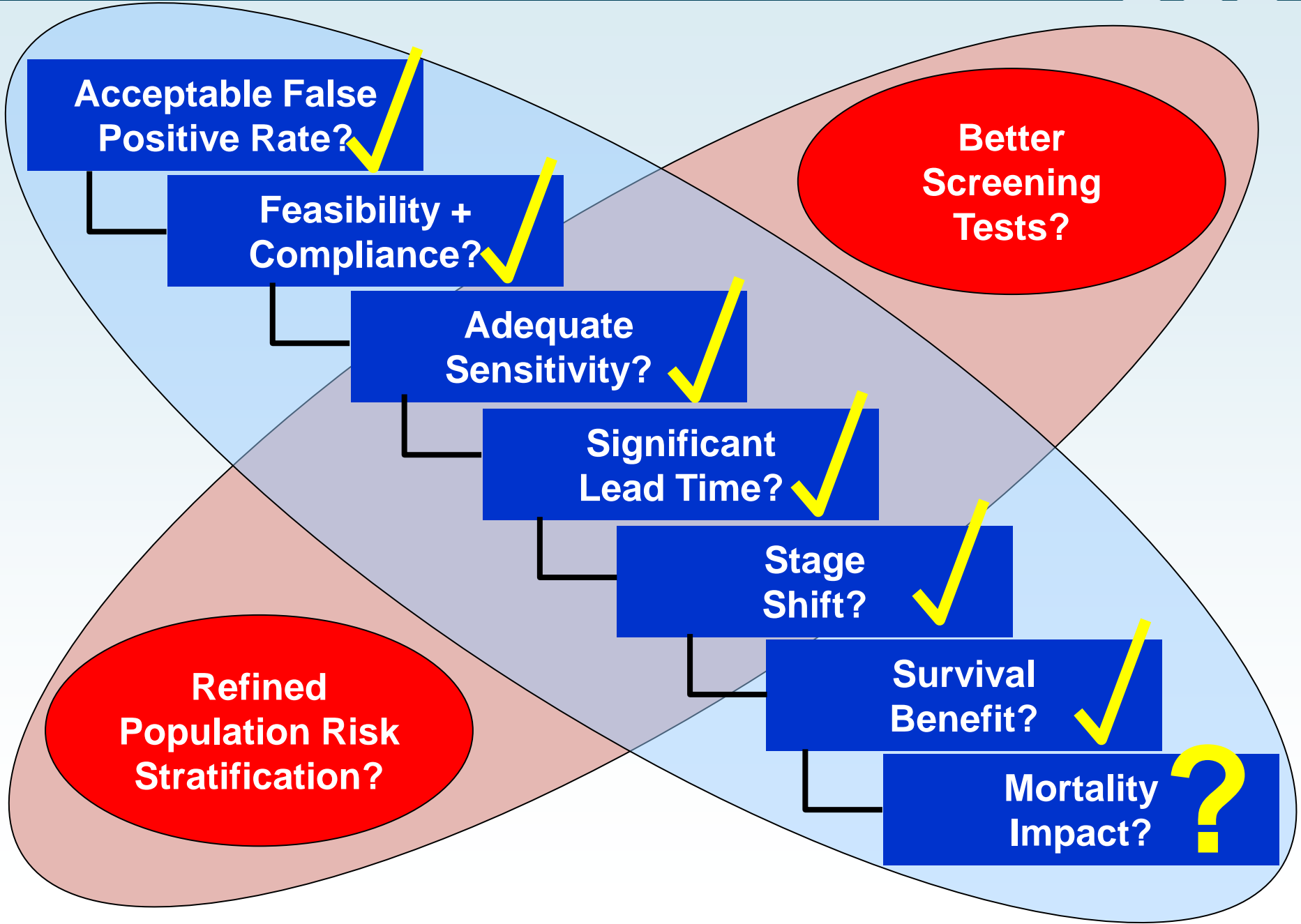
Adequate  
Sensitivity? ✓

Significant  
Lead Time? ✓

Stage  
Shift? ✓

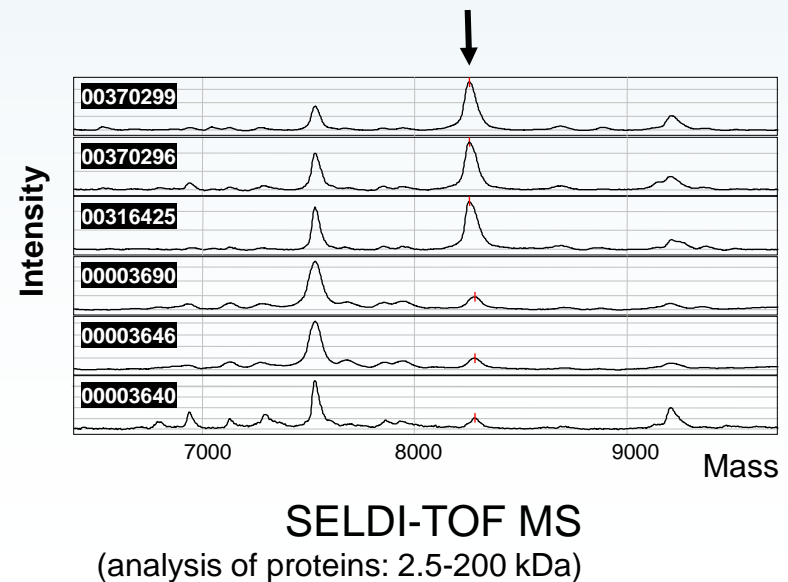
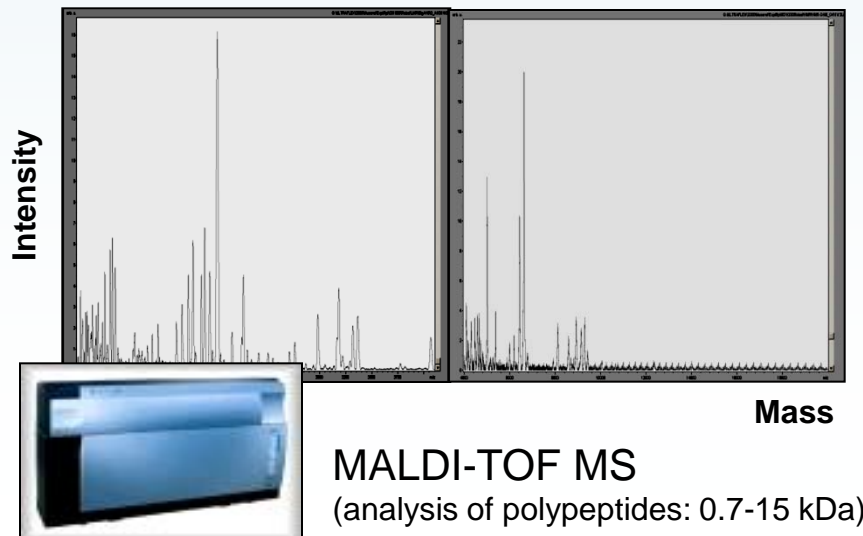
Survival  
Benefit? ✓

Mortality  
Impact? ?

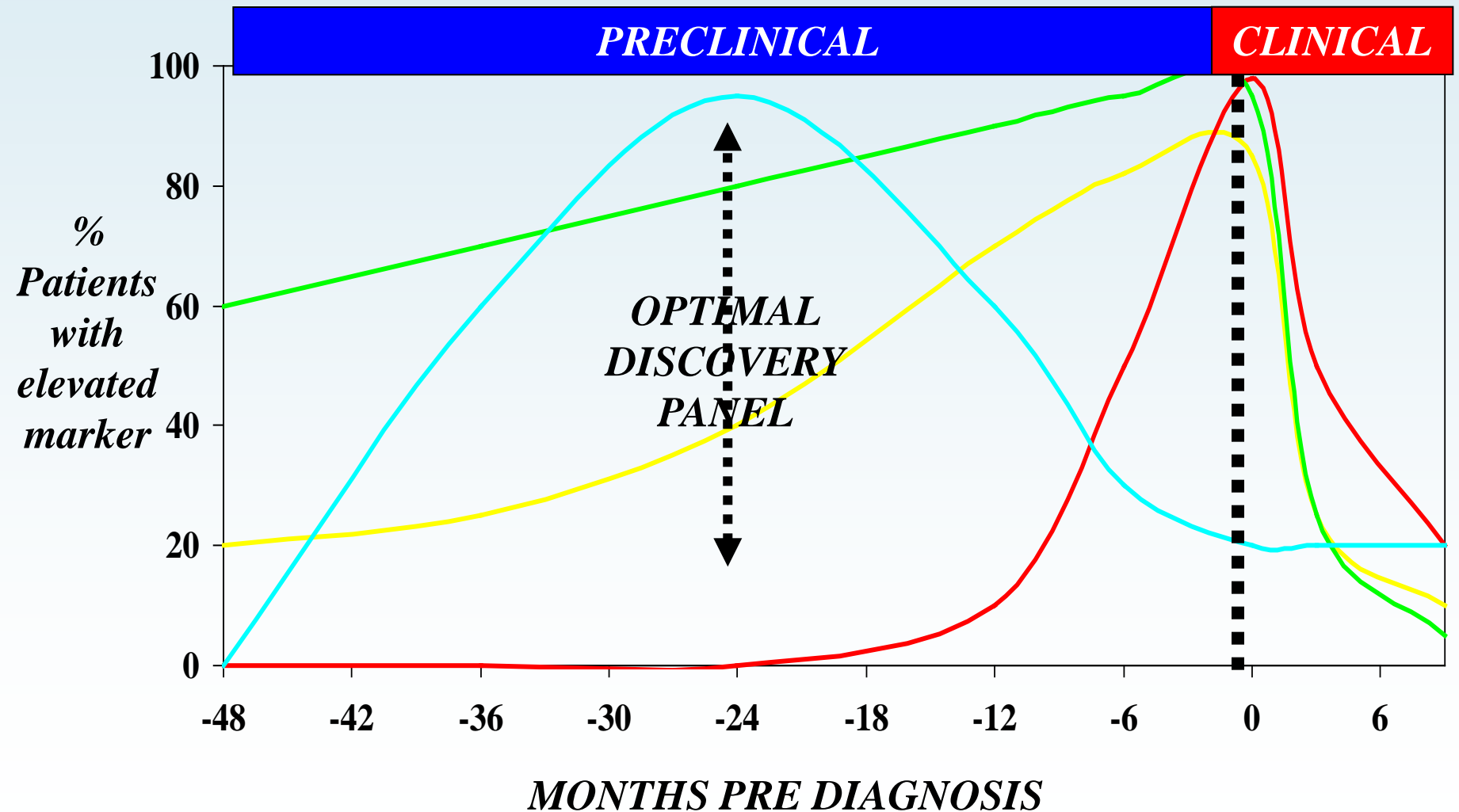


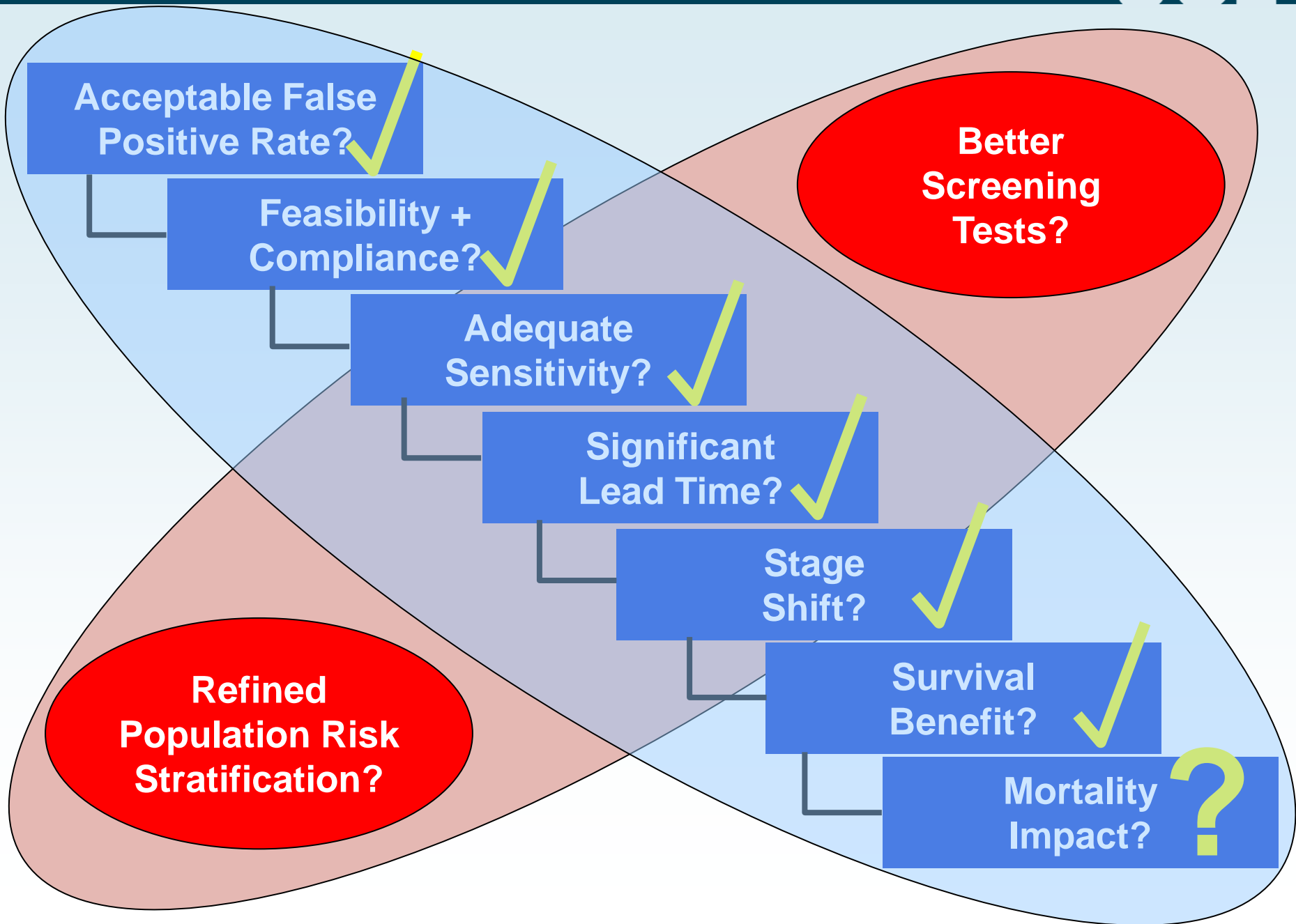
# Biomarker discovery

- ❑ 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



# BIOMARKERS WITH GREATER SENSITIVITY & LEAD TIME







# ACKNOWLEDGEMENTS - FUNDING

