What's next for ovarian cancer screening? Learning from UKCTOCS'

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MRC Clinical Trials Unit at UCL

18 January 2023 / ASGO Educational Webinars

Smarter Studies
Global Impact
Better Health

Disclosures

1. Institutional research collaborations in early detection of ovarian cancer with industry - RNA Guardian, Micronoma, Mercy Bioanalytics, Synteny

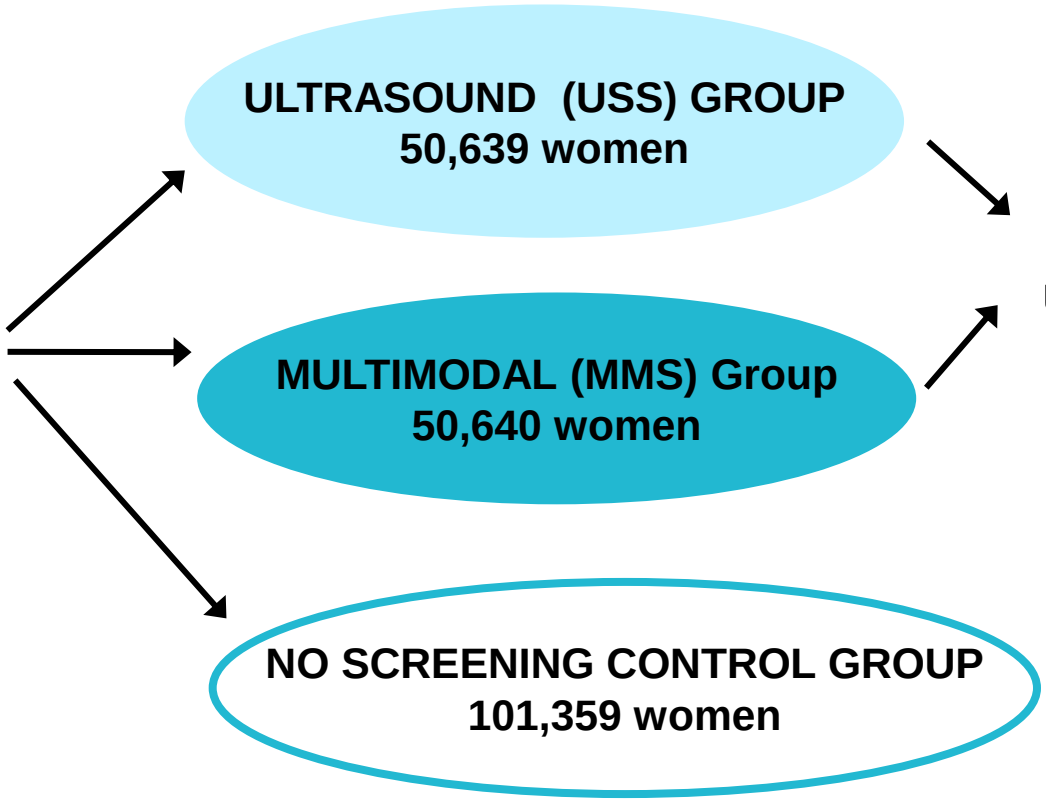
2. Research collaborations in early detection of ovarian cancer with UK, US and Australian academics supported by public and charity funded grants

UKCTOCS - Design

Multi-arm open label RCT

Women
- Aged 50-74
- With no periods
- One or both ovaries intact
- No high-risk family history

202,638 (2001-2005)



Annual screens until 31 Dec 2011

Primary outcome
Ovarian cancer Deaths

31 Dec 2014
30 June 2020

In parallel longitudinal psychosocial study

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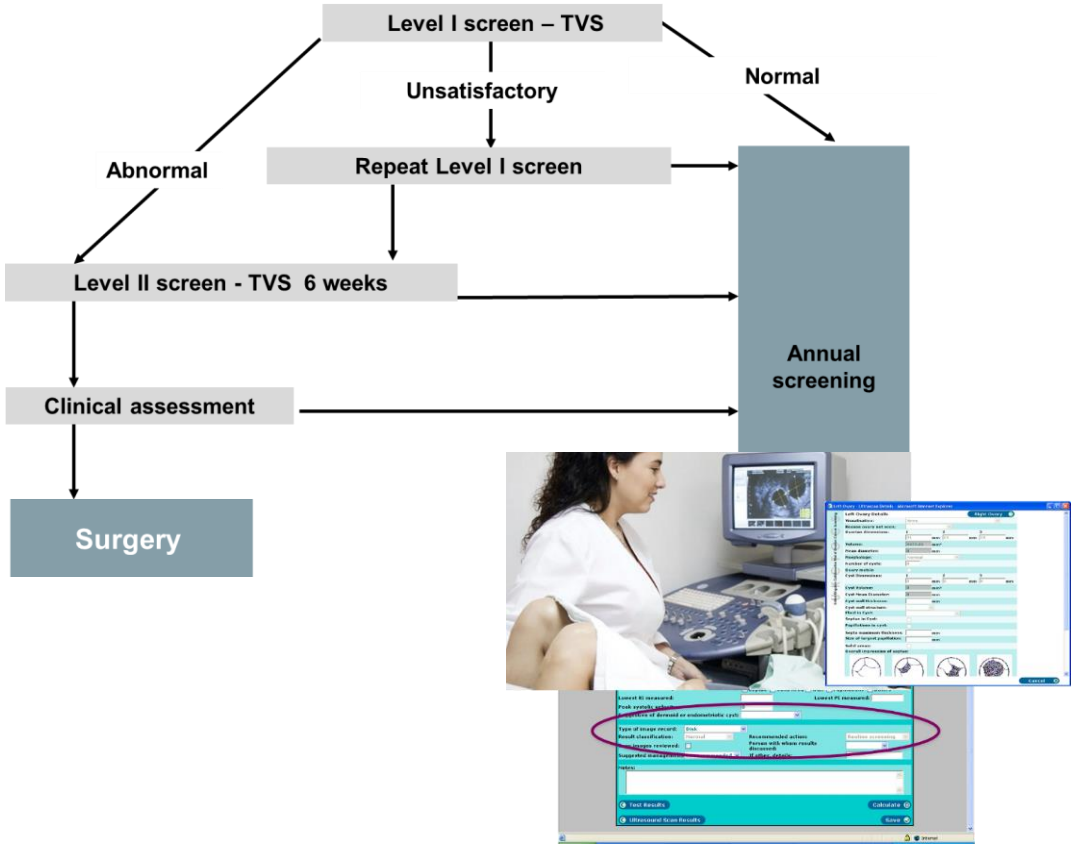
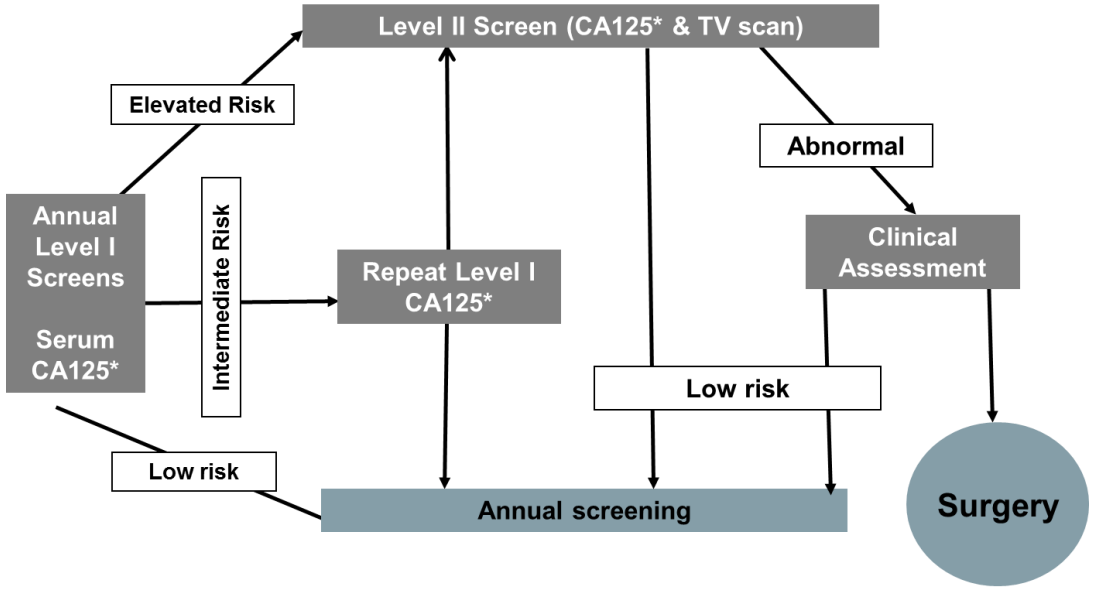
UKCTOCS – Screening strategies

Ultrasound Screening (USS)



Multimodal Screening (MMS)



*** Risk of Ovarian Cancer Algorithm**

Used Bayesian longitudinal Risk of Ovarian Cancer algorithm to interpret the CA125 levels

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UKCTOCS - Conduct

Multicentre

Invitation through NHS registers

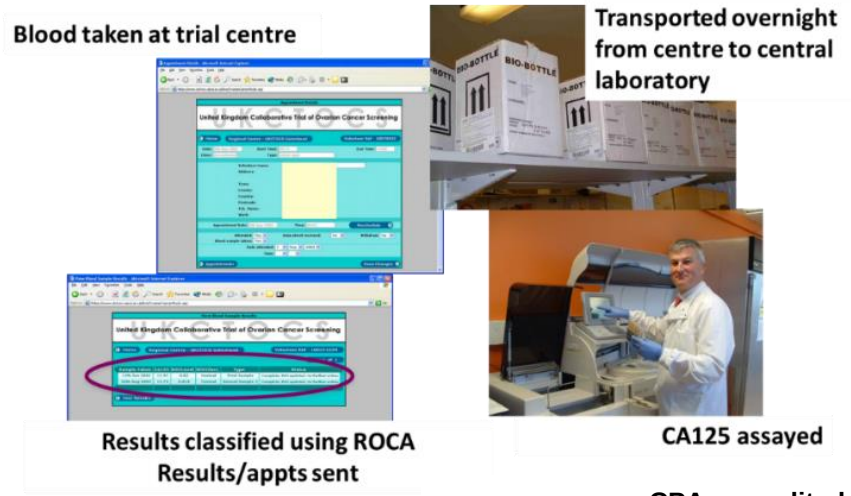
Electronic bespoke trial management system with automation of many aspects of protocol implementation

Electronic health records linkage using NHS number - complete follow-up in 95% on 30 June 2020

Outcomes review of all potential ovarian or tubal cancers by review committee blinded to randomisation group

27 Primary Care Trusts
3185 GP practices

Conduct of MMS screening



CPA accredited
CA125 external QA scheme

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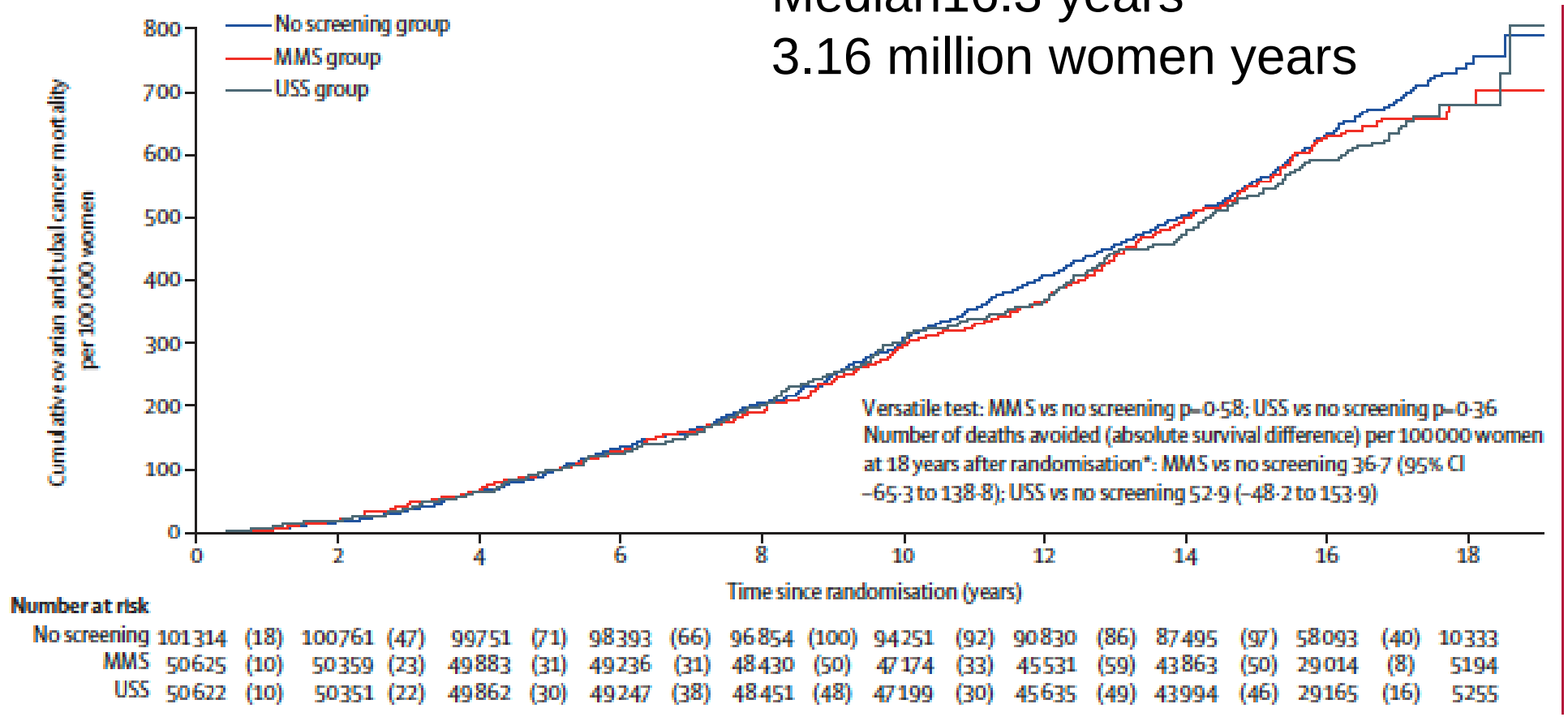
Deaths due to ovarian and tubal cancer

Follow up
Median16.3 years
3.16 million women years



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Secondary outcomes MMS - ovarian and tubal cancers

MMS Performance	
Annual screens	345,570
Median annual screens per women	**8 (7-11)**
Compliance	81%
Sensitivity	**84%**
Specificity	**99.8%**
Positive predictive value	29%
Unnecessary (false positive) surgery	
Per 10,000 annual screens	**14**
Per ovarian cancer detected	2
Complication rate in above	3%

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Secondary outcomes MMS - ovarian and tubal cancers

MMS versus no screening control

Intention to screen analysis 9.5 years after end of screening
Median follow up from randomisation- 16.3 years

Incidence - no difference

Stage incidence rates
Decrease in Stage III/IV incidence rates - 10·2% (–21·3 - 2·4)

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Ovarian and tubal cancer

International classification of disease (ICD)

- Malignant neoplasm of ovary (ICD10-C56)
  - Non epithelial ovarian cancers
  - Borderline epithelial ovarian cancer
  - Invasive Epithelial Ovarian Cancer
    - Mucinous
    - Clear cell
    - Endometriod
    - Low grade serous
    - **High grade serous**

Majority of deaths
High grade serous ovarian and tubal cancer

- **Malignant neoplasm of Fallopian Tube (ICD10 – C57.0)**
- **What used to be previously classified as Malignant neoplasm of peritoneum (ICD10 – C48.1)**

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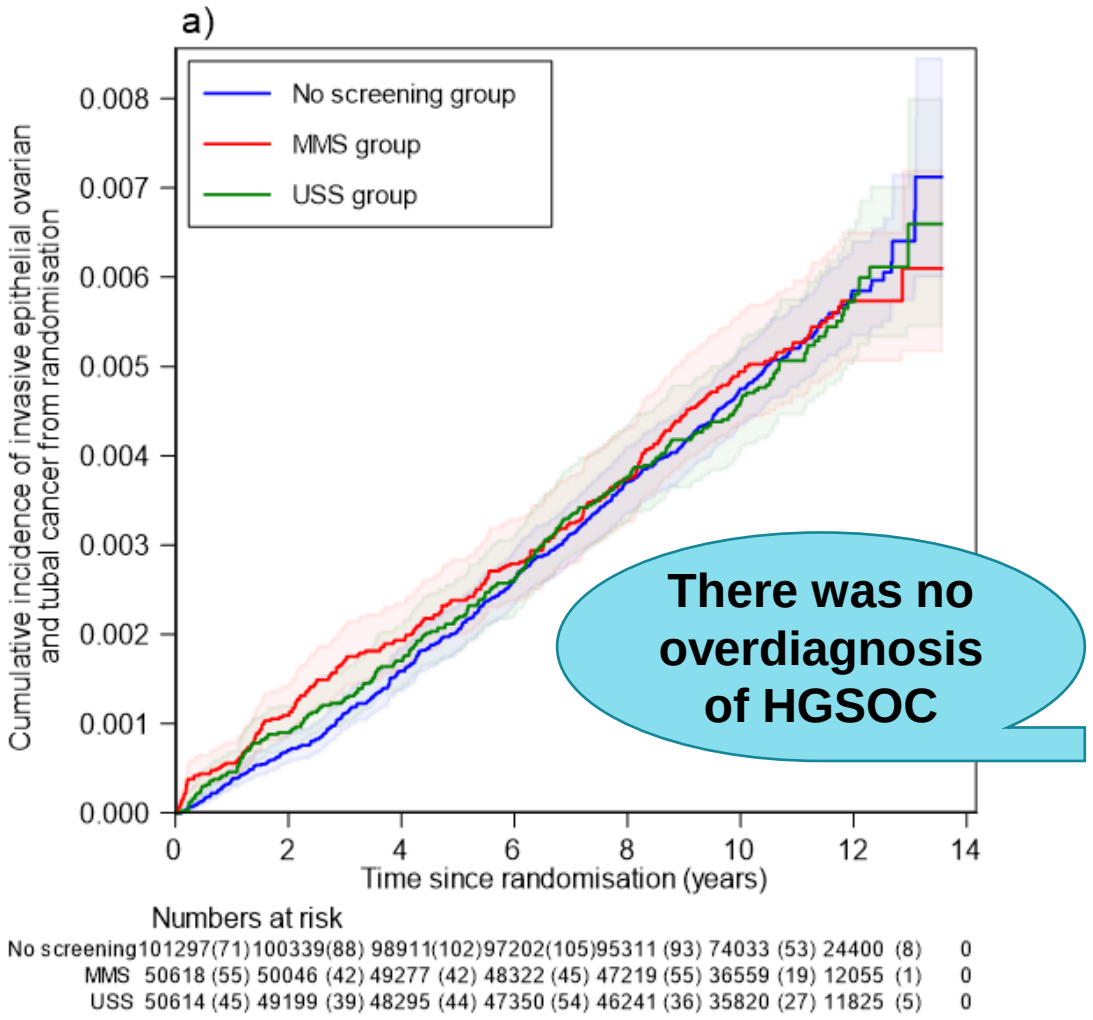
HGSOC Incidence till 31 Dec 2014

1029 (85%) of 1209 women with invasive epithelial ovarian cancer had HGSOC

The incidence was the same in all arms

MMS - 259 (0·5%) of 50,625

No screening - 520 (0·5%) of 101,314



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HGSOC Incidence and Stage

HGSOC in C and MMS groups till 31st Dec 2014

(85% of invasive cancers)

Characteristics of women with high grade serous ovarian/tubal cancer (HGSOC) diagnosed between

Characteristic, No. (%)	No screening (C) group	Multimodal (MMS) group		
	Clinically diagnosed	Screen detected	Clinically diagnosed	*p-value**
Randomised and eligible women	101 314	50 625		
Cancers by screening status	520 (0·51)	153 (0·30)	106 (0·21)	
Cancers by Intention to screen	520 (0·51)	259 (0·51)		p=1·000
FIGO 2014 III/IV/Unable to stage by screening status	446 (86)	107 (70)	88 (83)	*p<0·0001*
FIGO 2014 III/IV/Unable to stage by Intention to screen	**446 (86)**	**195 (75)**		***p=0·0003***

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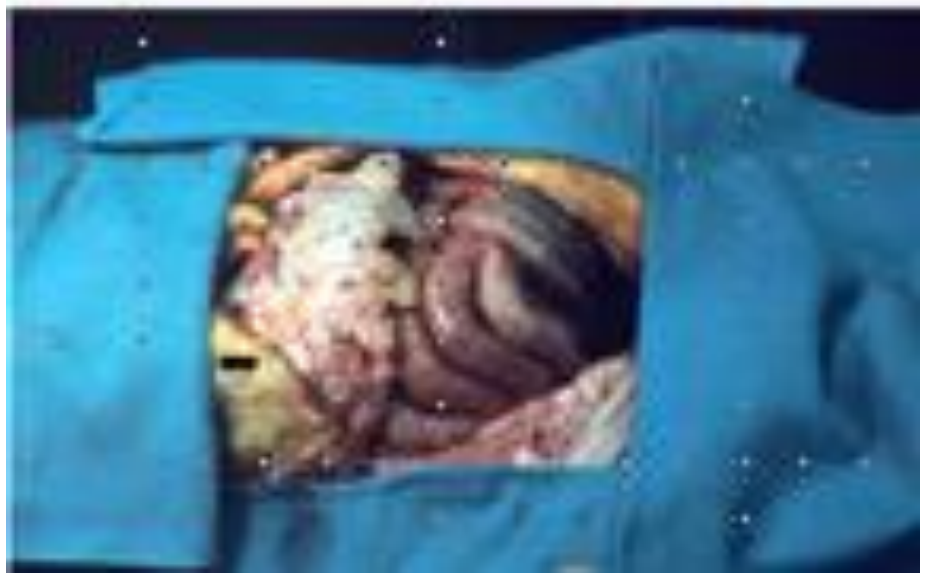
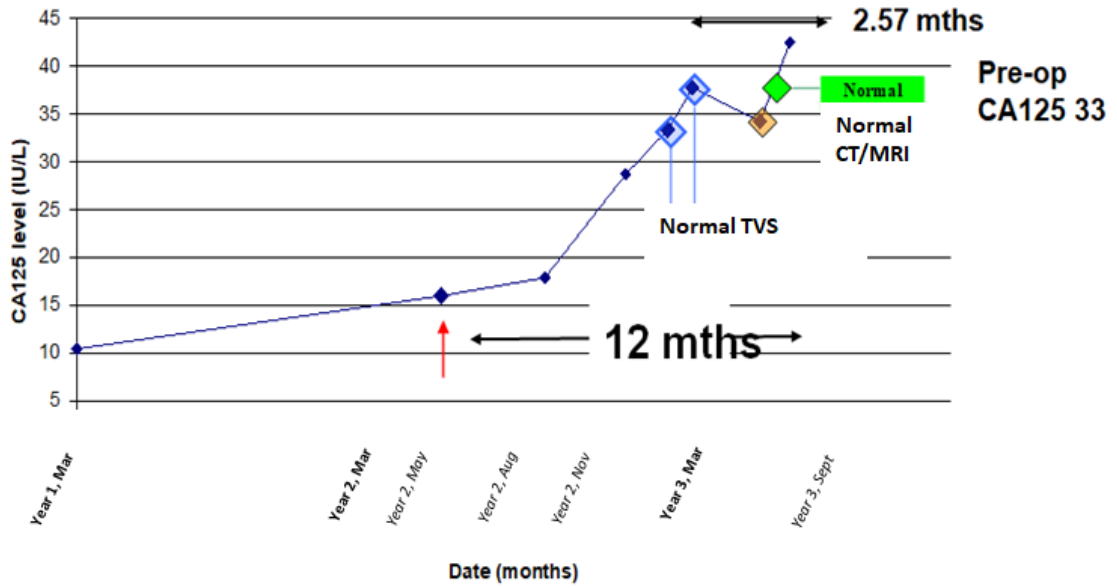
HGSOC - Tumour volume

Evidence that tumour volume was less in MMS group



Clinically diagnosed Stage IIIB

High grade serous ovarian cancer: **IIIB**
Pathology: Right ovary 3x1.5x1.5 cm with tumour breaching the capsule and extending into the paratubal connective tissue. Left ovary 4x3x1 cm with deposits within the stroma and surface.. 3 small <0.5 cm white nodules in deep pelvis. Previous hysterectomy.



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HGSOC - Tumour volume and surgical outcomes

Characteristics of women with high grade serous ovarian/tubal cancer (HGSOC) diagnosed between				
Characteristic, No. (%)	**No screening (C) group**	**Multimodal (MMS) group**		
	Clinically diagnosed	**Screen detected**	**Clinically diagnosed**	***p-value****
Primary surgery by screening status	219 (42)	119 (78)	39 (37)	
Primary surgery by intention to screen	**219 (42)**	**158 (61)**		**p<0·0001**
Zero residual after surgery by screening status	157 (30)	84 (55)	35 (33)	
Zero residual after surgery on intention to screen	**157 (30)**	**119 (46)**		**p<0·0001**

Evidence that tumour volume was less and surgical outcomes were better in MMS group

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HGSOC – First line treatment

10% Increase in women receiving surgery and chemo

No increase in proportion of women receiving platinum and taxol

Characteristics of women with high grade serous ovarian/tubal cancer (HGSOC) diagnosed between

Characteristic, No. (%)	No screening (C) group	Multimodal (MMS) group		
	Clinically diagnosed	Screen detected	Clinically diagnosed	*p-value**
Treatment in women with stage 1a and 1b* **	**14**	**11**	**3**	
Surgery & Chemo by screening status	9 (64)	6 (55)	2 (66)	
Surgery & Chemo by intention to screen	9 (64)	8 (57)		p=0·710
Combination chemotherapy** by screening status	3 (21)	1(9)	1(33)	
Combination chemotherapy** by intention to screen	3 (21)	2(14)		p=0·632
Treatment in women with stage ≥ Ic	**506**	**142**	**103**	
Surgery & Chemo by screening status	322 (64)	127 (89)	57 (55)	
Surgery & Chemo by intention to screen	**322 (64)**	**184 (74)**		**p=0·006**
Combination chemotherapy** by screening status	290 (57)	92 (65)	48 (47)	
Combination chemotherapy** by intention to screen	290 (57)	140 (57)		p=1·000

Need to increase focus on treatment of cancers especially screen detected cancers

Since end of screening in the trial, newer more effective agents have been licensed

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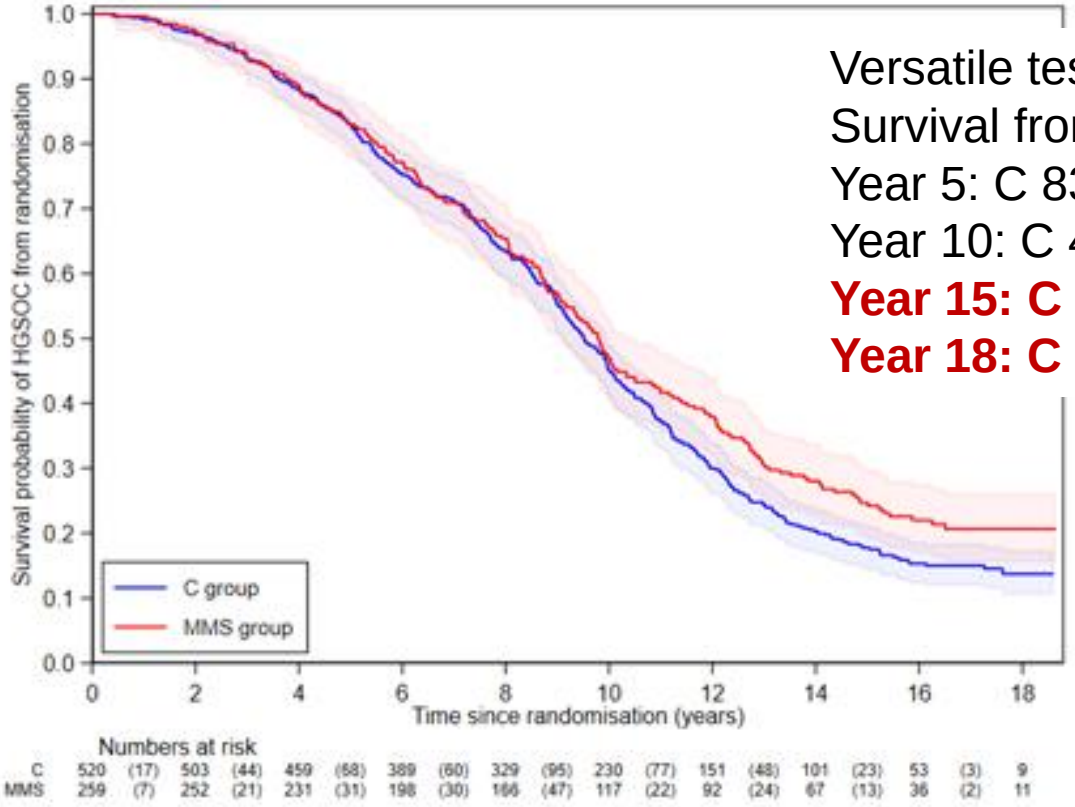
HGSOC - Survival from randomisation

Survival from randomisation (with 95% confidence bands) of women with HGSOC diagnosed till 31 Dec 2014 and followed up till 30 June 2020 by Group

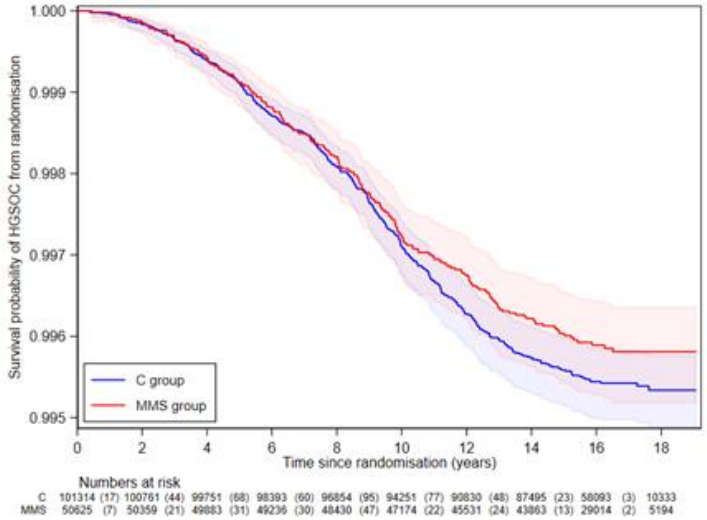
A. Denominator – only women with HGSOC



Versatile test C vs MMS **p=0.042**
Survival from randomisation
Year 5: C 83% MMS 83%
Year 10: C 45% MMS 46%
Year 15: C 17.5% MMS 24%
Year 18: C 14% MMS 21%

B. Denominator – all randomised women

Versatile test
C vs MMS p=0.286



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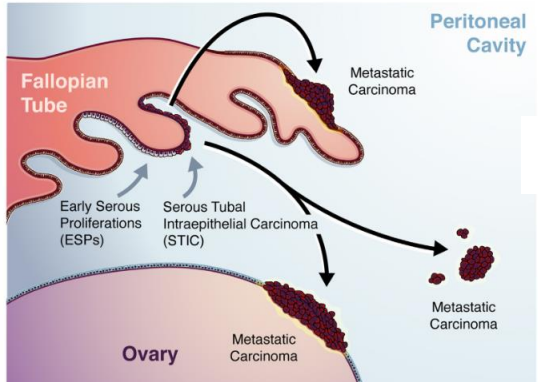
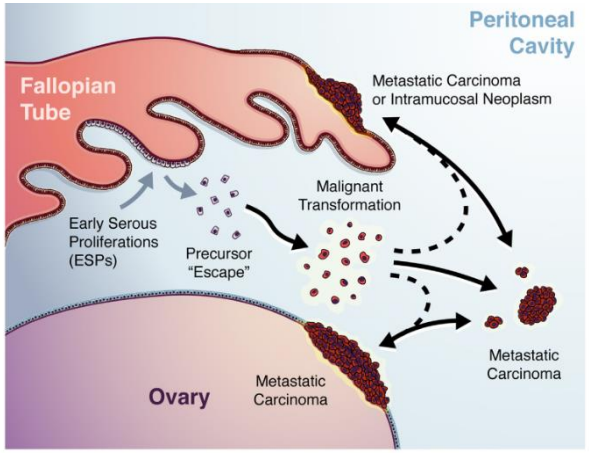
Evolution of HGSOC

Multiple complementary pathways



Fallopian tubal theory

'Precursor escape' theory



TR Soong et al Gynae Oncol 2019

During most of the pre-clinical period
<1 cm in diameter

Spends approximately 1 year as stage III / IV cancers before they become clinically apparent

Brown P0, Palmer C PLoS Med 2009

UKCTOCS Median FU 11.1 years
Only 28 Stage 1a/1b HGSOC
2.7% (14/520) in no screening
5.4% (14/259, p=0.057) in MMS

Larger stage shifts potentially require detection of very early lesions including STICS

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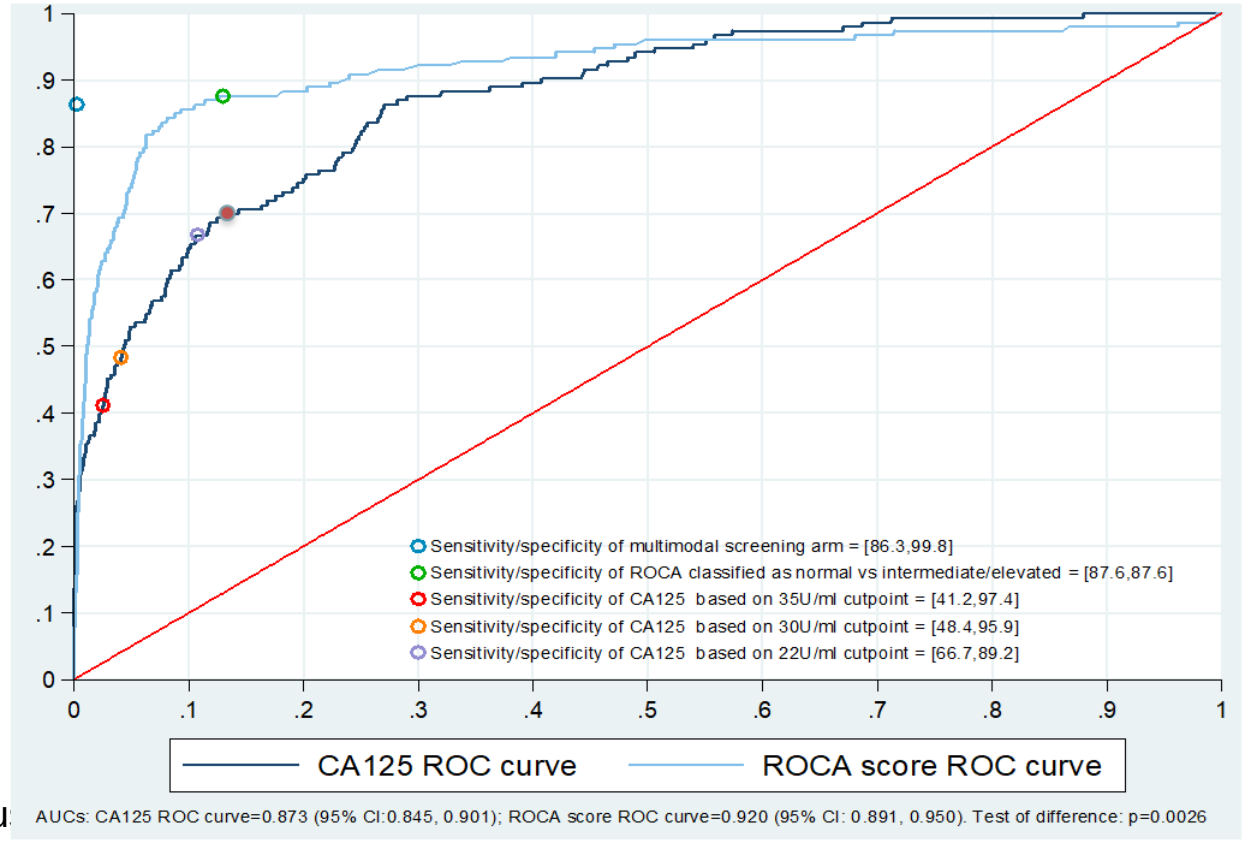
Improved performance with longitudinal biomarker algorithms

Multimodal Screening (MMS)

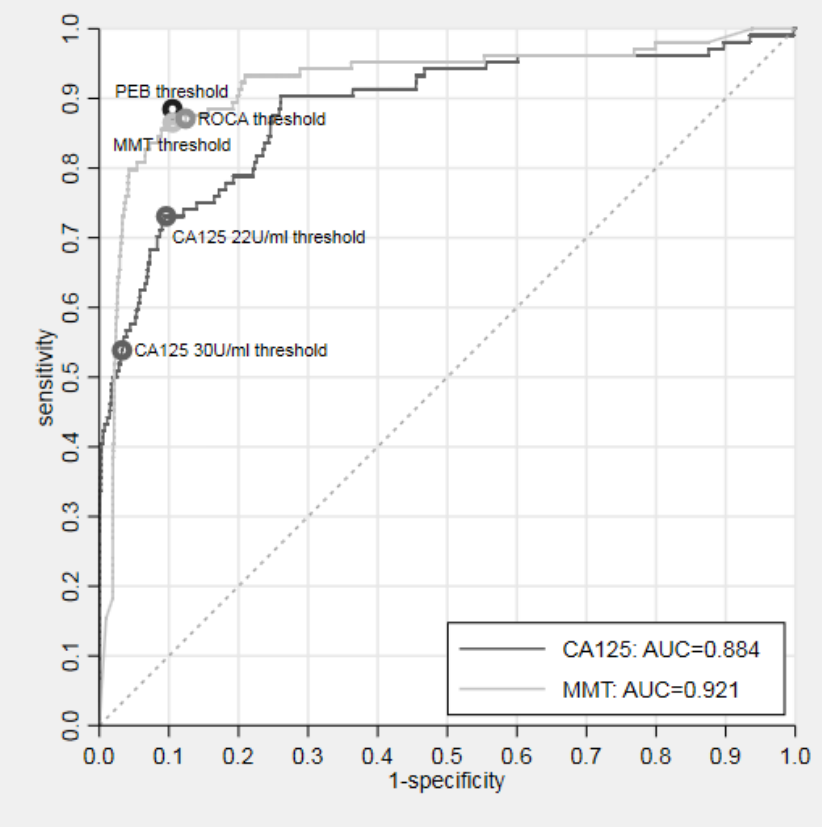


ROC
versu
screening

Half the cases of invasive epithelial ovarian and tubal cancer would not have been detected at that annual screen if CA125 cut-off of 35 had been used

Menon et al JCO June 2015

Improved Performance with longitudinal CA125 algorithms



At a specificity of 89.5%, sensitivity

MMT 86.5% (95%CI: 78.4-91.9)

PEB (PARAMETRIC EMPIRICAL BAYES) 88.5% (95%CI: 80.6-93.4)

WERE SIMILAR TO ROCA

Sensitivity 87.1%; specificity 87.6%

AND SIGNIFICANTLY HIGHER THAN

SINGLE CA125 THRESHOLD 73.1% (95%CI: 63.6-80.8)

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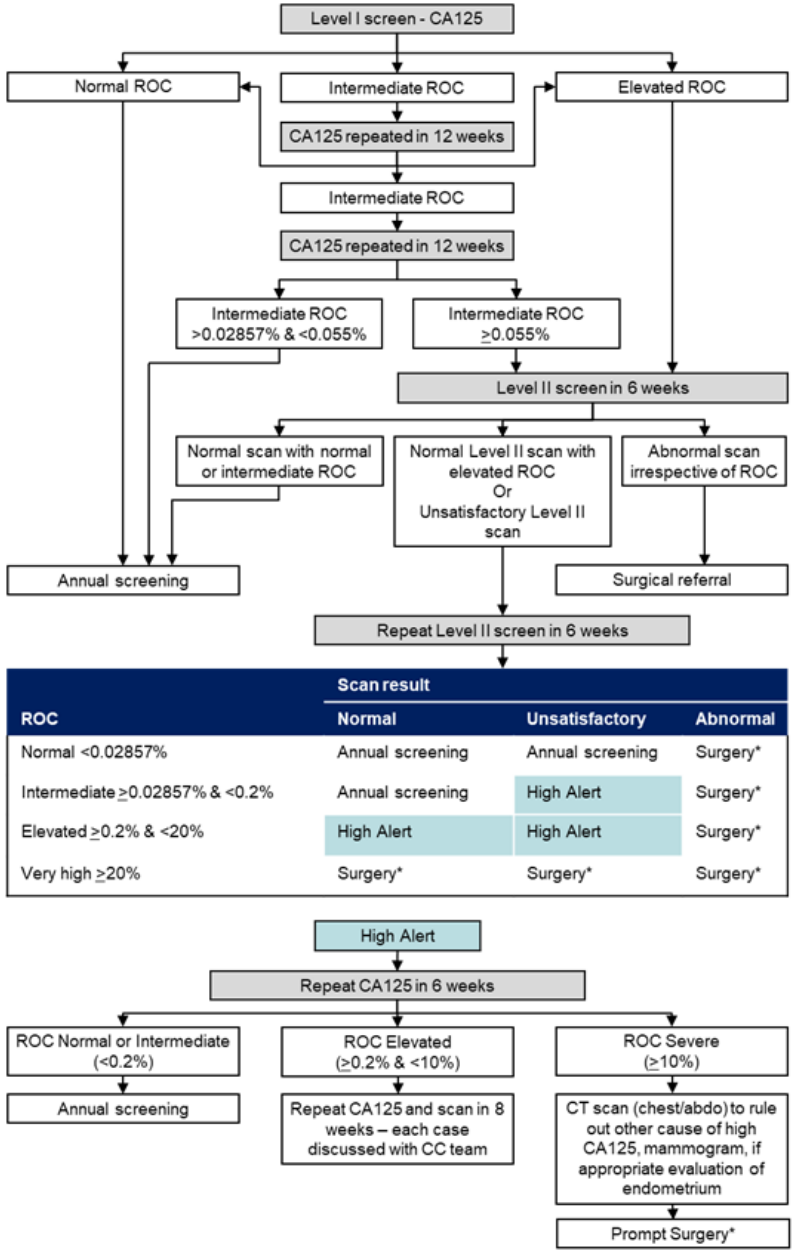
Blyuss O et al. Clinical Cancer Research, 2018

MMS screening strategy

CA125 had to be repeated to reach required specificity of 99.8%

Transvaginal ultrasound scans were repeatedly negative when CA125 values low

In women with SEVERE risk on the CA125 ROCA operated despite negative imaging



	Scan result		
ROC	Normal	Unsatisfactory	Abnormal
Normal <0.02857%	Annual screening	Annual screening	Surgery*
Intermediate ≥0.02857% & <0.2%	Annual screening	High Alert	Surgery*
Elevated ≥0.2% & <20%	High Alert	High Alert	Surgery*
Very high ≥20%	Surgery*	Surgery*	Surgery*

Menon U et al JCO 2015

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Time interval from annual screen to diagnosis

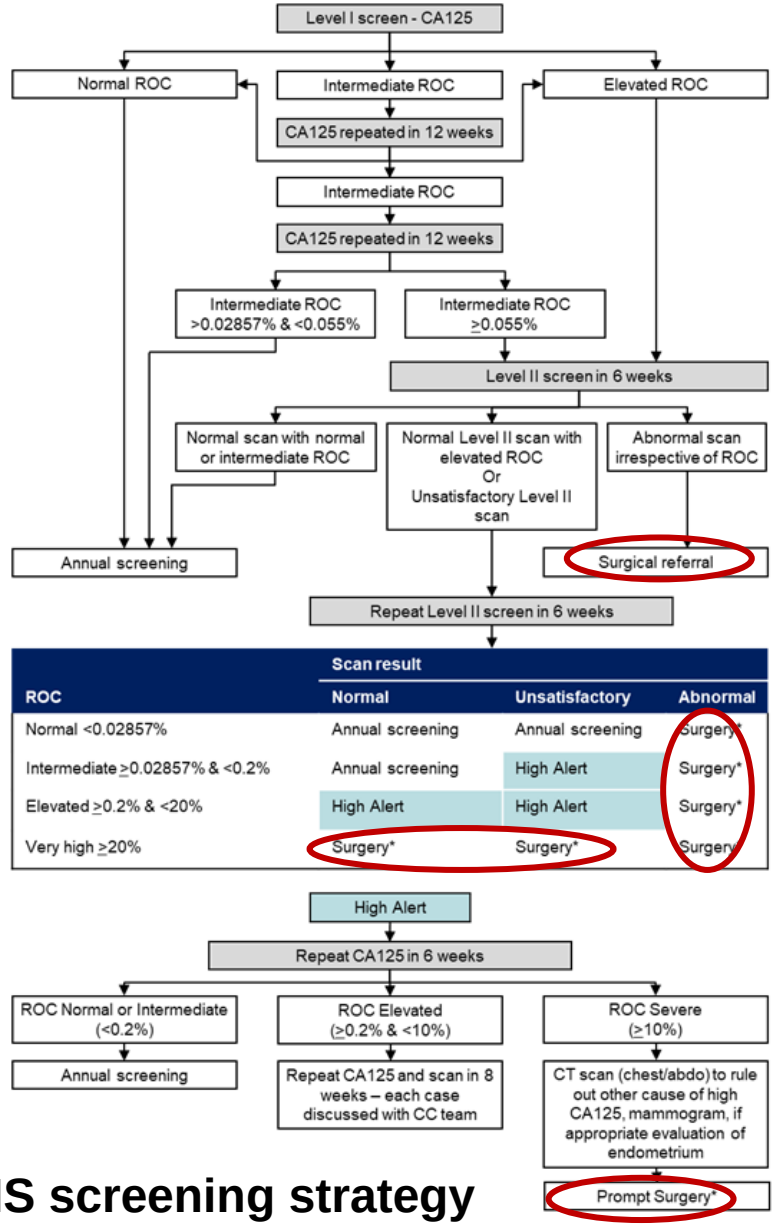
In women with screen-detected invasive epithelial OC

Median time from annual abnormal ROCA screen to diagnosis (usually NHS surgery)

All: 20 weeks

Annual CA125 >35: 12 weeks

Annual CA125 ≤ 35: 30 weeks



MMS screening strategy

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Menon U et al JCO 2015

UKCTOCS bioresources

Valuable bioresource to support future research

- Screening data
- Longitudinal follow up data
- Baseline and longitudinal biosamples

Several nested case-control biomarker projects on early detection of cancer

544,808 serum samples (500µL aliquots)

- 189,642 baseline samples 189,452 women
- 355,166 annual serial samples (median 9) 50,262 women in the blood group

UKCTOCS Longitudinal Women's Cohort (UKLWC)

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http://uklwc.mrcctu.ucl.ac.uk/

Need - Cohorts for evaluating new biomarkers

Immediate need so that performance of novel biomarkers can be independently validated prior to inclusion in an ovarian cancer screening trial

Cohort I - To assess sensitivity for early detection

Moderate to High risk opting for risk reducing surgery
Age ≥35 years 2,500 - 5,000

Single sample (blood, vaginal, uterine samples)
~100-250 mainly high-grade serous cancers
(Based on incidence 4-5% occult high grade serous cancers, more than half Stage I or pre-malignant)

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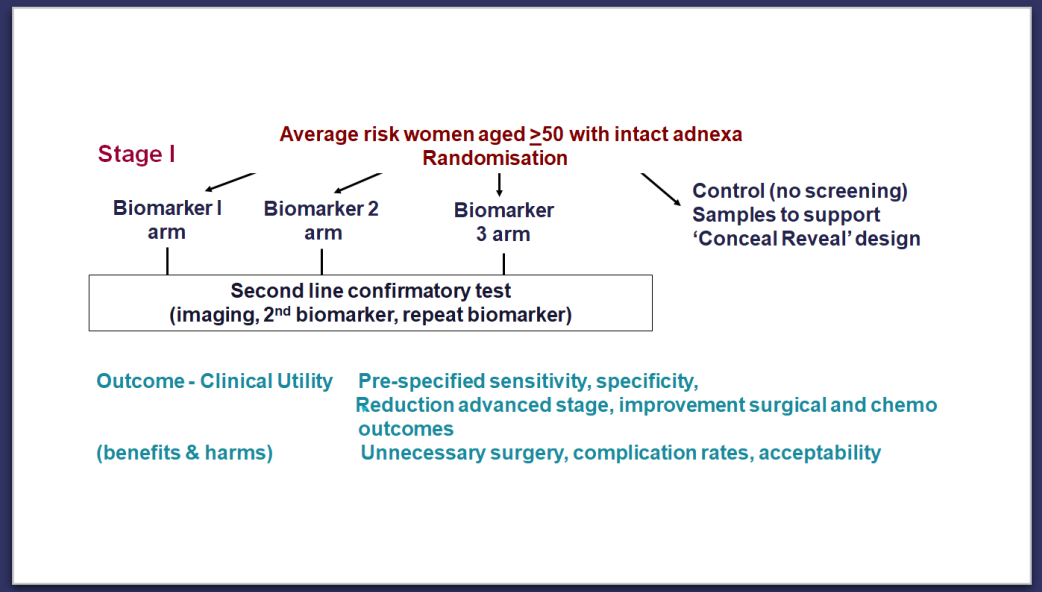
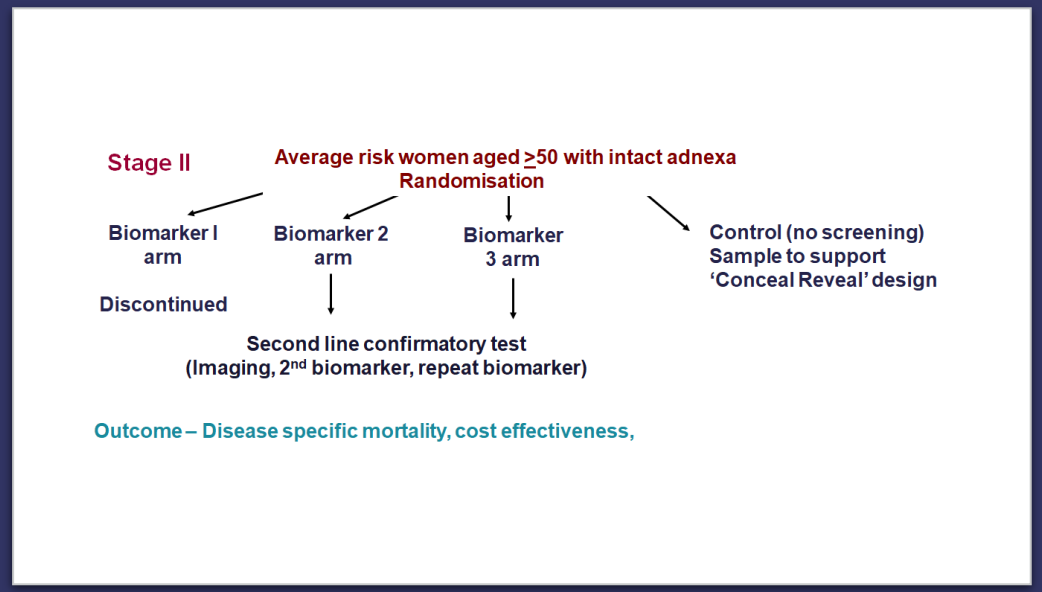
Future ovarian cancer screening trials

- Target population for future screening trials
  - Risk stratification using newer risk prediction algorithms
  - Given the changing risk thresholds, likely to be women at intermediate risk (in high-risk, risk reducing surgery)

- New trial designs
  - Multistage, multi-arm adaptive randomised controlled trial,
  - Non-randomised stepped wedge design,
  - RCT with ‘Conceal Reveal’ design – Nested mortality

- Need to consider treatment of screen detected cancers





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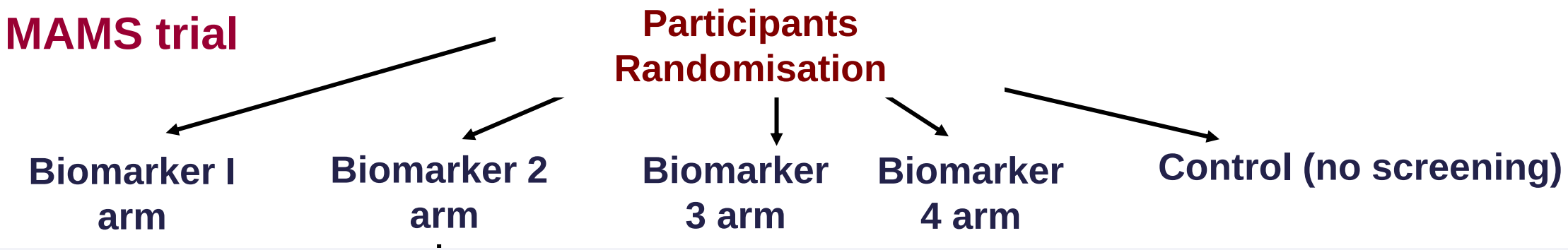
Increasing efficiency of screening RCTs



Update on National Cancer Institute (NCI) Vanguard Study on Multi-Cancer Detection

As a central component of the Cancer Moonshot[SM], the National Cancer Institute is launching a new research network to study cancer screening, including evaluating the effectiveness of new blood tests for the detection of one or more cancers to prevent cancer-related deaths. If found to be useful, these new blood tests provide the opportunity for less invasive tools for the early detection of cancer. In 2024, NCI will begin enrolling 24,000 healthy people aged 45-70 in a Vanguard study to lay the groundwork for the later, larger study. The Vanguard study is being funded in part by 21st Century Cures Act Cancer Moonshot funds.

Increasing efficiency of screening RCTs

Surrogate end points for mortality

Incidence of late-stage cancer (NHS Galleri trial)
Modelling impact of stage on mortality
Incidence of metastatic disease and cancer deaths

However, most health care systems, regulatory agencies, and guideline bodies still require evidence of reduced mortality before approving tests for marketing, reimbursement, or widespread use

Summary

Screening in UKCTOCS did not reduce deaths due to ovarian cancer - ovarian cancer screening cannot be recommended for the general population

However, UKCTOCS provides evidence that

- screening can detect HGSOC earlier
- stage alone does not capture the magnitude of early detection
- screening improves surgical treatment outcomes
- longitudinal biomarker algorithms improve performance of screening tests
- imaging as a second line test currently does not have the required sensitivity

The trial bioresources provide the opportunity to evaluate some of the novel biomarkers

Future research

Our findings suggest that future technologies able to detect **more women** with high-grade serous cancer **earlier**, **coupled with treatment improvements**, likely to impact on disease mortality in the future.

Cumulative results suggest that surrogate endpoints for disease-specific mortality, such as advanced stage or better treatment outcomes, should not currently be used in place of disease-specific mortality in ovarian cancer screening trials

The UKCTOCS screening data is invaluable for modelling ovarian cancer screening as are the samples for evaluating novel early detection markers

Acknowledgements

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CANCER RESEARCH UK

Women who took part

Artwork
Dr Lizzie Burns.

Each dot represents 8 of the 202,638 women who participated in UKCTOCS

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ROCA risk cut-offs

27 Primary Care Trusts
3185 GP practices

Risk calculated using the ROCA algorithm that was automated – based on age and CA125 levels

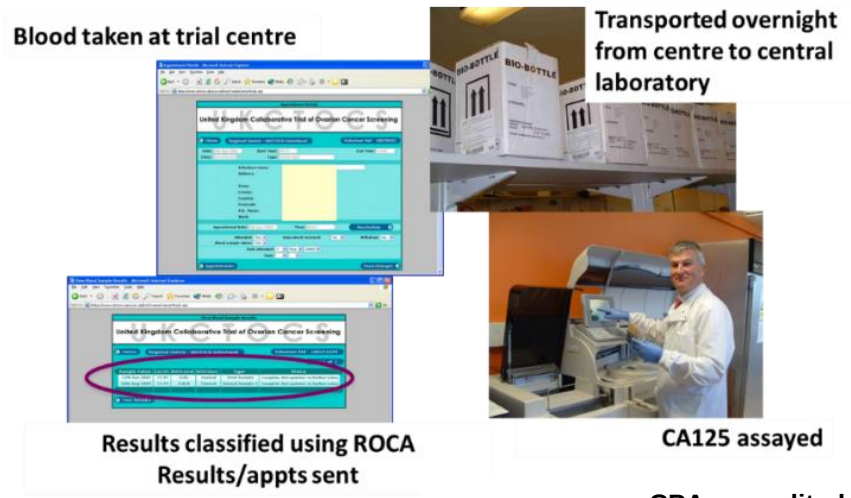
Normal risk
ROCA estimate of OC diagnosis of <1 in 3500)

Intermediate risk
ROCA estimate of OC diagnosis of <1 in 1000 and >1 in 3500)

Elevated risk
ROCA estimate of OC diagnosis of ROC >1 in 1000

Severe risk
ROCA estimate of OC diagnosis of ROC ≥1 in 20

Conduct of MMS screening



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CA125 external QA scheme

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Non-HGSOC Morphology

Characteristics of women diagnosed between recruitment and 31 December 2014 with non-HGSOC - 15% of invasive cancers)

	No screening (C) group	Multimodal (MMS) group		Utrasound (USS) group	
	C: Clinically diagnosed	MMS: Screen detected	MMS: Clinically diagnosed	USS: Screen detected	USS: Clinically diagnosed
Characteristics, No. (%)	**93**	**27**	**25**	**24**	**10**
Morphology	**93 (50%=46.5)**	**52**		**34**	
Endometrioid, low grade	25 (27)	10 (37)	8 (32)	5 (21)	2 (20)
Clear Cell	21 (23)	5 (19)	11 (44)	11 (46)	1 (10)
Serous, low grade	19 (20)	11 (41)	1 (4)	5 (21)	3 (30)
Mucinous	25 (27)	1 (4)	5 (20)	3 (13)	4 (40)
Mixed Cell	2 (2)				
Brenner	1 (1)				

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Non-HGSOC Stage at diagnosis

Characteristics, No. (%)	C: Clinically diagnosed 93	MMS: Screen detected 27	MMS: Clinically diagnosed 25	USS: Screen detected 24	USS: Clinically diagnosed 10
FIGO 2014 Stage					
Stage I	62 (67)	20 (74)	20 (80)	17 (71)	5 (50)
Stage II	12 (13)	3 (11)	2 (8)	3 (13)	
Stage III	16 (17)	3 (11)	3 (12)	4 (17)	4 (40)
Stage IV	3 (3)	1 (4)			1 (10)
Advanced stage (III/IV/unable to stage) by screening status	19 (20)	4 (15)	3 (12)	4 (17)	5 (50)
Advanced stage (III/IV/unable to stage) on Intention to screen*	19 (20)	7 (13)		9 (26)	

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