Principles of screening & diagnostics in ovarian cancer

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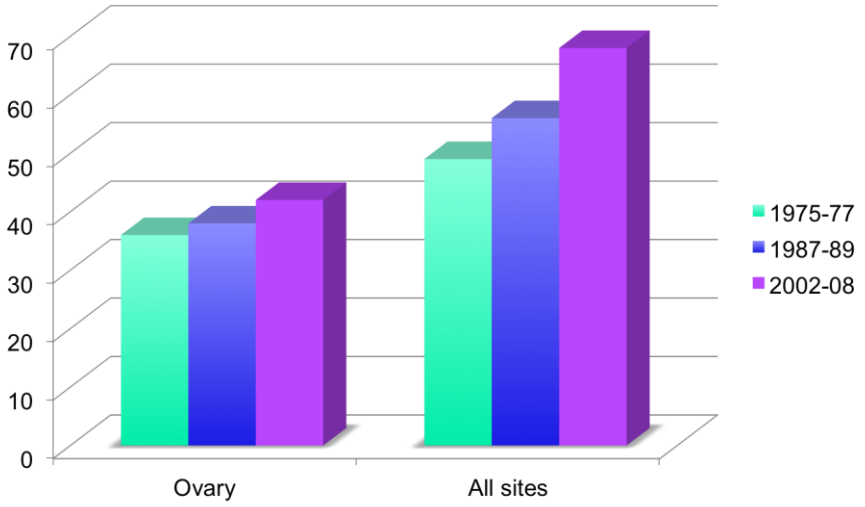
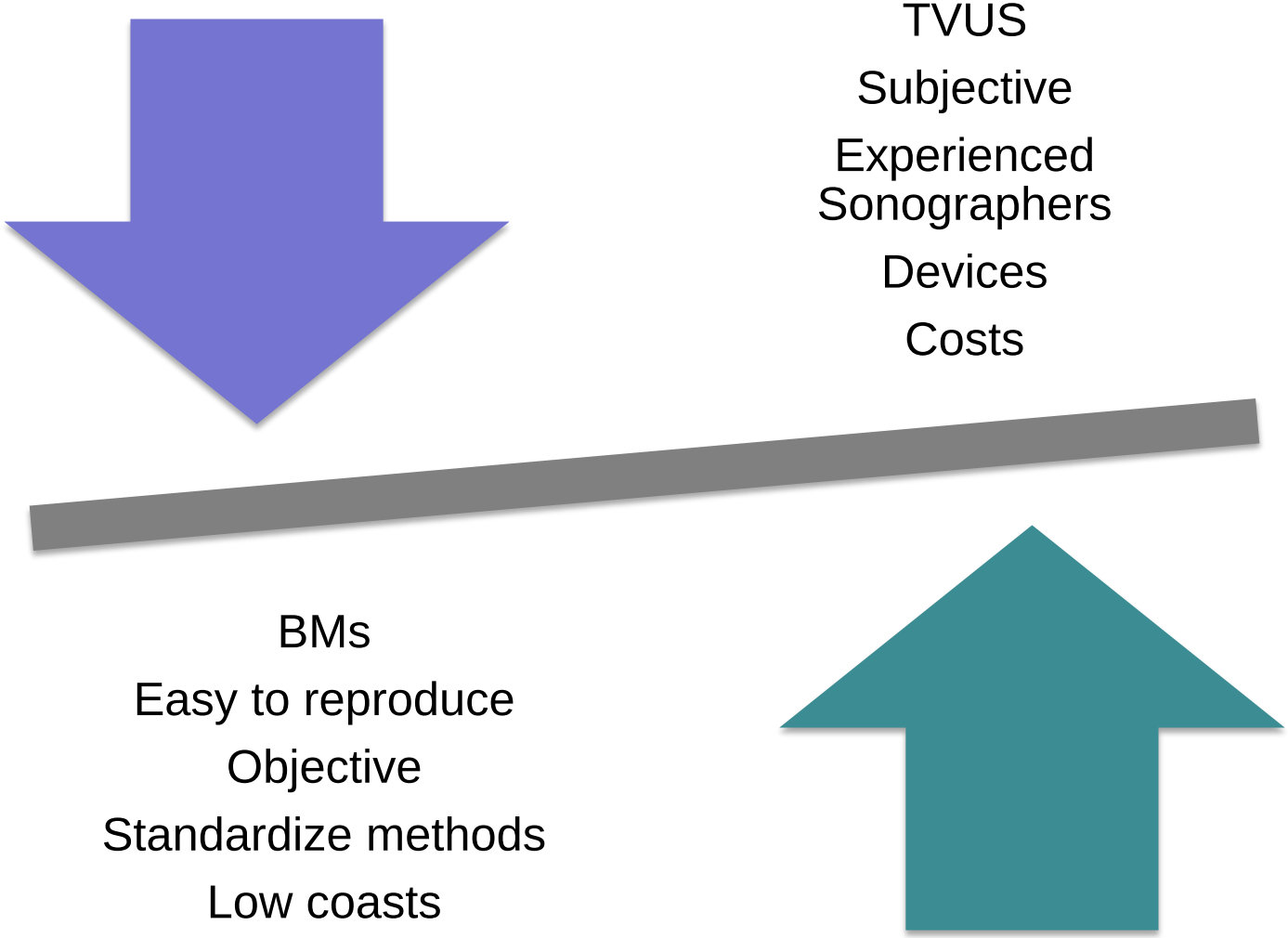
NOGGO

Ovarian Cancer

- silent killer
- presents late
- poor prognosis
- Since the late 1980s there has been a steady improvement in 5-year survival
- Survival rates between 30% and 40%
- allow diagnosis of early stages in asymptomatic patients

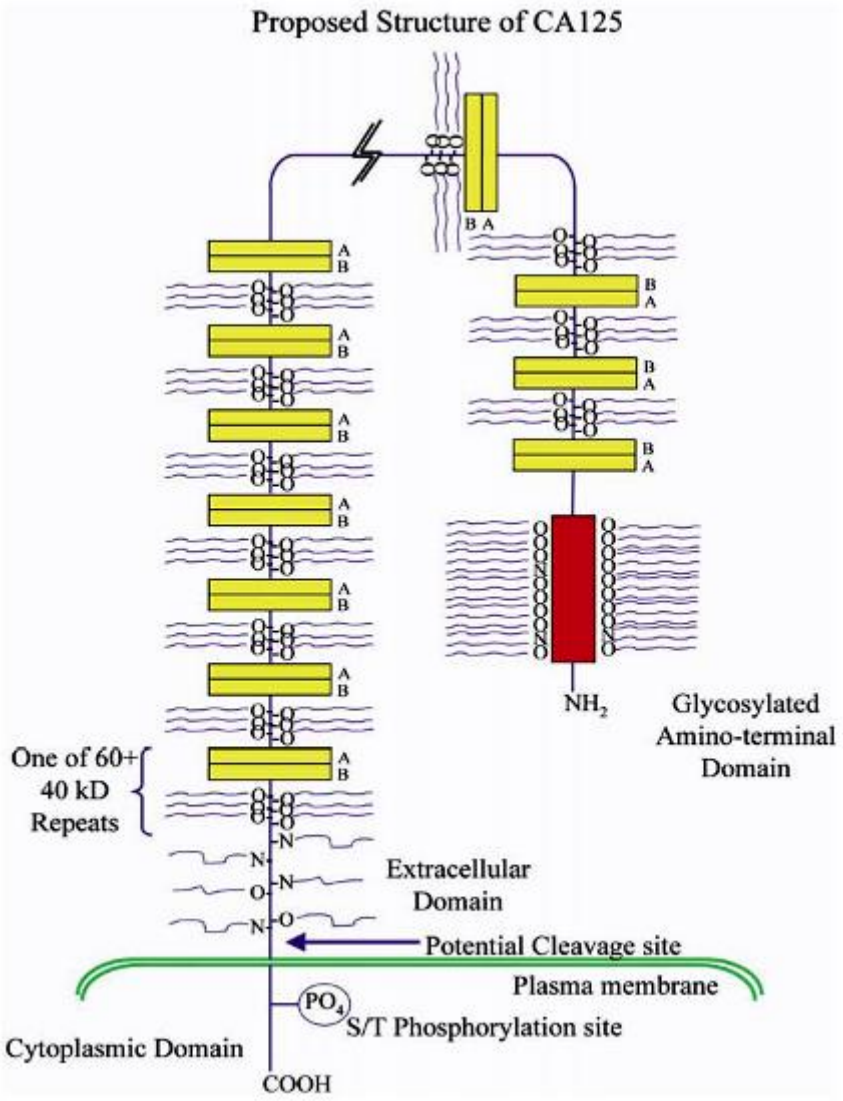


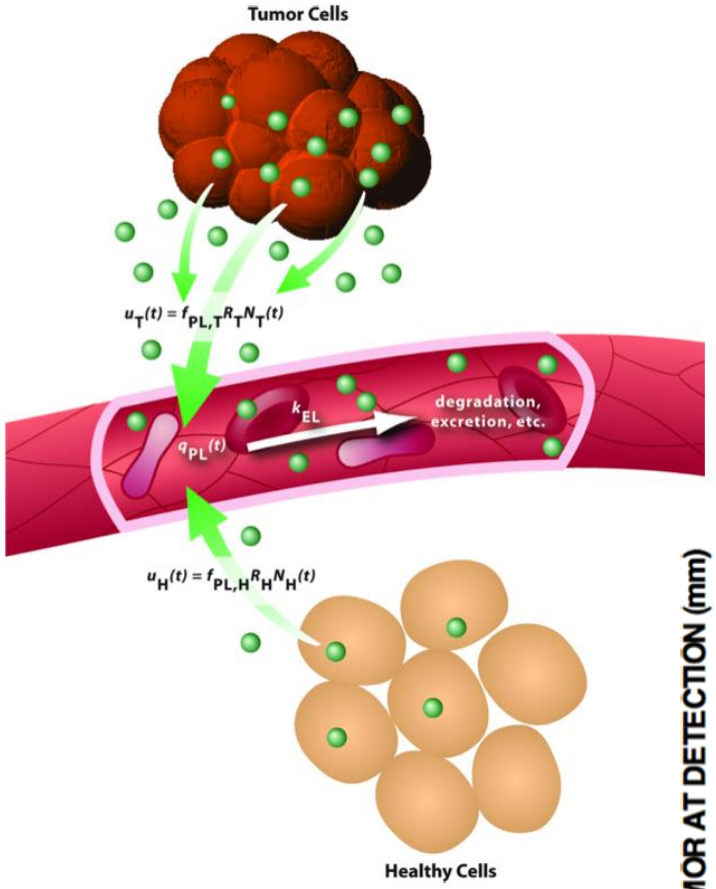

TVUS
Subjective
Experienced Sonographers
Devices
Costs
BMs
Easy to reproduce
Objective
Standardize methods
Low coasts

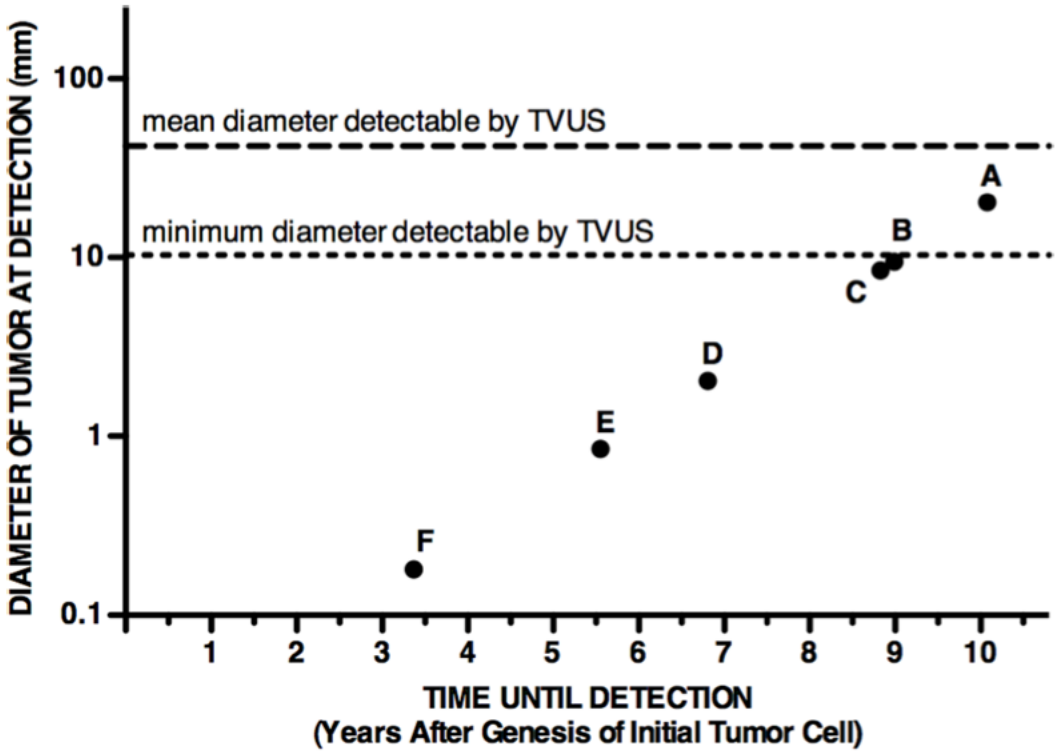
Screening

CA125

- Circulatory levels increased in 80% of OvCa patients and in 1% of healthy women
- In FIGO-stage I only in 50% of the cases





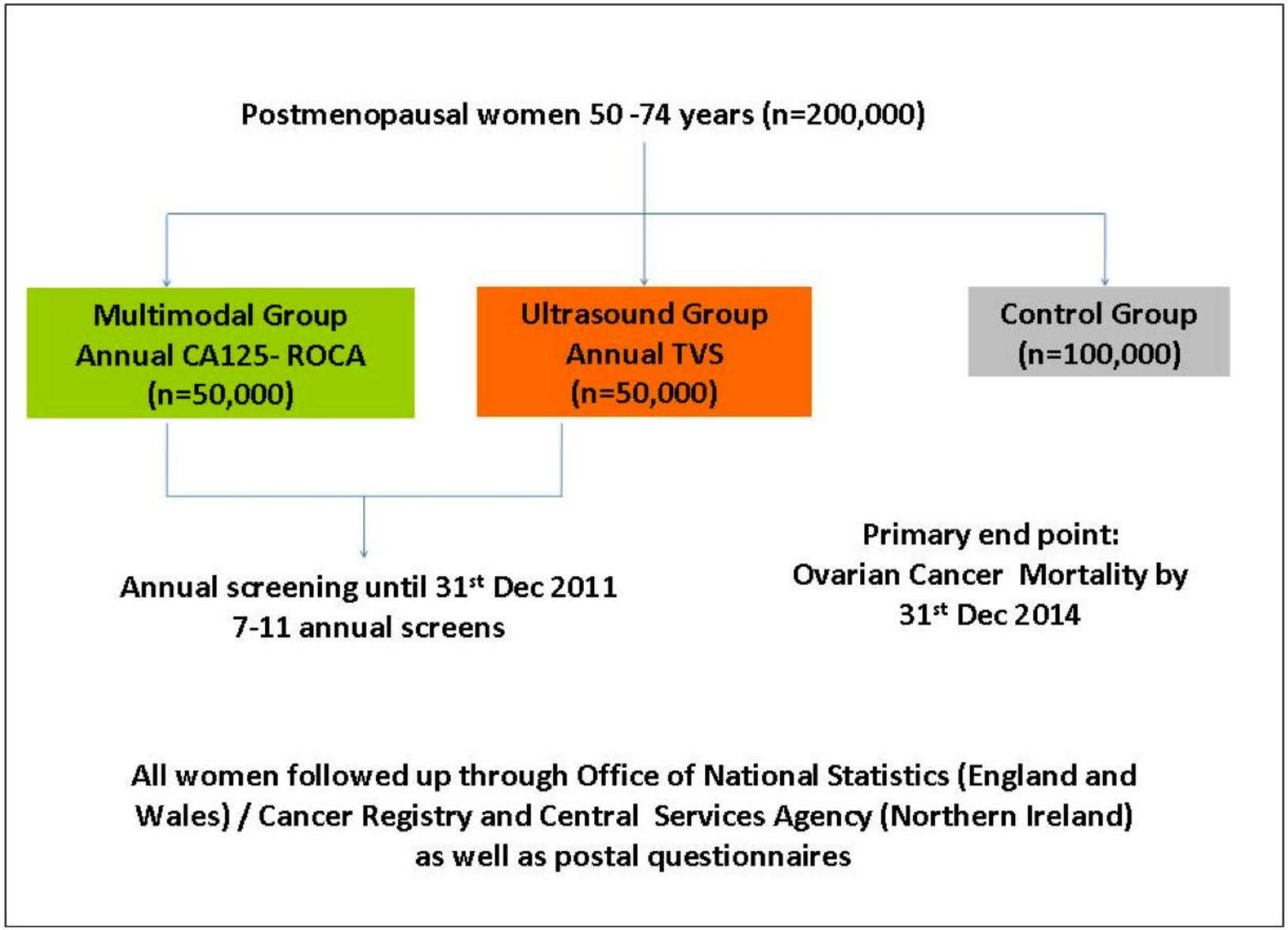


Hori et al 2011

Risk of ovarian cancer algorithm (ROCA)

- Computerized algorithm
- Compares each individuals CA125 profile to the pattern in ovarian cancer and healthy women
- The closer the profile to known cases of ovarian cancer, the greater the risk for ovarian caner
- Produces each individuals percentage risk of having ovarian cancer

UKCTOCS Trial



UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

	MMS	USS	Overall
N Op	97 (0.2%)	845 (1.8%)	942 (1.0%)
N Op/OC	2.9	35.2	16.2
Sensit.	89.5%	75%	82.9%
Specif.	99.8%	98.2%	99%
PPV	35.1%	2.8%	6.2%
Stage			
I	14	10	24
II	2	2	4
III	18	10	28
IV	0	2	2
OC (I/II)	47.1%	50.0%	48.3%

Menon et al. The Lancet 2009

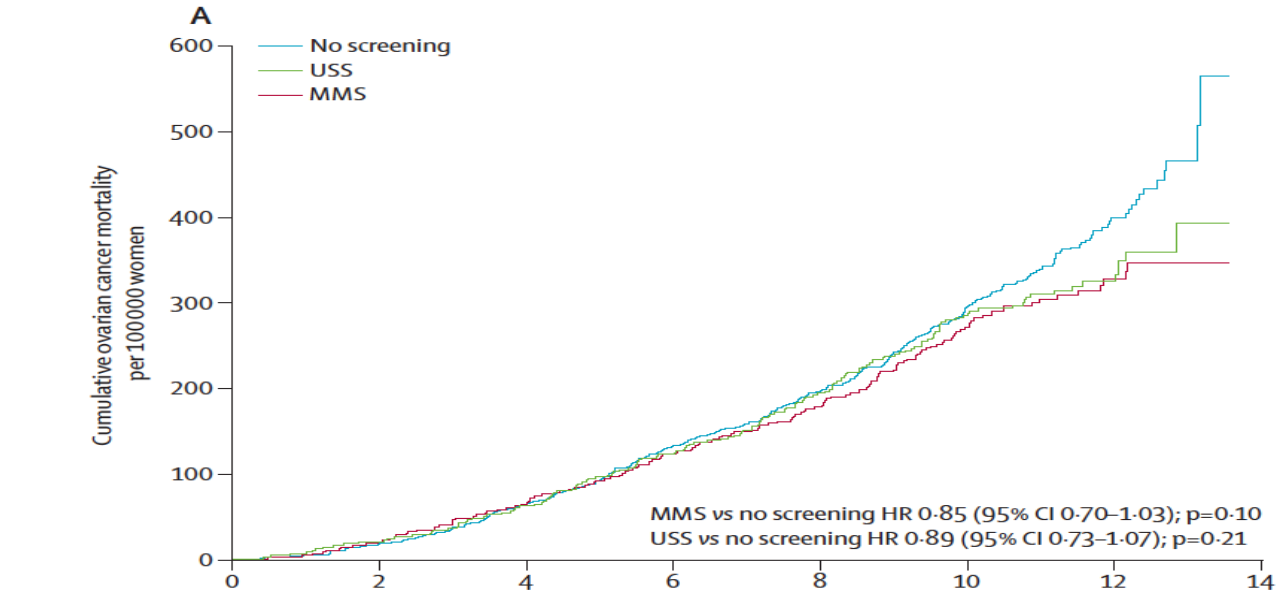
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Ian J Jacobs, Usha Menon*, Andy Ryan, Aleksandra Gentry-Maharaj, Matthew Burnell, Jatinderpal K Kalsi, Nazar N Amso, Sophia Apostolidou, Elizabeth Benjamin, Derek Cruickshank, Danielle N Crump, Susan K Davies, Anne Dawnay, Stephen Dobbs, Gwendolen Fletcher, Jeremy Ford, Keith Godfrey, Richard Gunu, Mariam Habib, Rachel Hallett, Jonathan Herod, Howard Jenkins, Chloe Karpinskyj, Simon Leeson, Sara J Lewis, William R Liston, Alberto Lopes, Tim Mould, John Murdoch, David Oram, Dustin J Rabideau, Karina Reynolds, Ian Scott, Mourad W Seif, Aarti Sharma, Naveena Singh, Julie Taylor, Fiona Warburton, Martin Widschwendter, Karin Williamson, Robert Woolas, Lesley Fallowfield, Alistair J McGuire, Stuart Campbell, Mahesh Parmar†, Steven J Skates†*

Summary

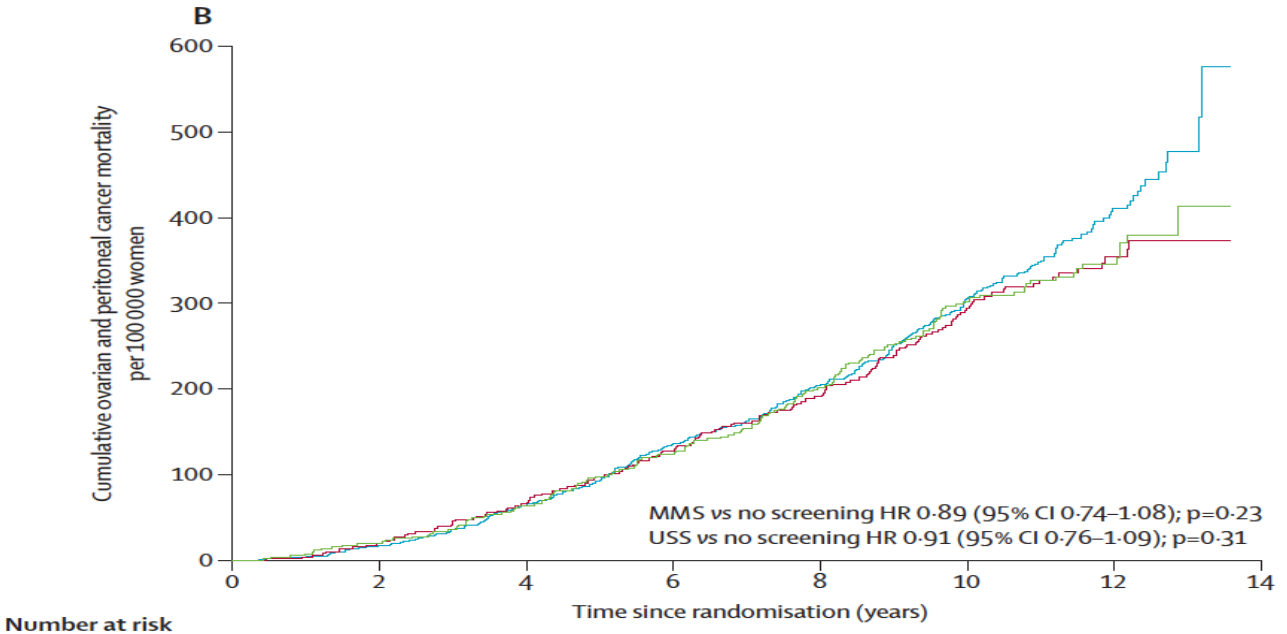
Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Published Online December 17, 2015



Number at risk

No screening	101 299	100 720	99 662	98 238	96 632	75 582	25 252
MMS	50 624	50 343	49 846	49 176	48 345	37 758	12 592
USS	50 623	50 338	49 838	49 192	48 363	37 768	12 689



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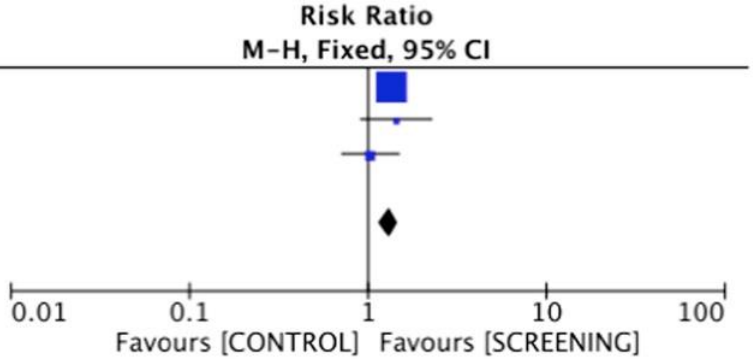
Risk of ovarian cancer at an early stage

Study or Subgroup	SCREENING Events	SCREENING Total	CONTROL Events	CONTROL Total	Weight	Risk Ratio M-H, Fixed, 95% CI
UKCTOCS 2015	277	652	198	630	78.2%	1.35 [1.17, 1.56]
SCOCS 2007	22	35	14	32	5.7%	1.44 [0.90, 2.29]
PLCO 2011	47	212	38	176	16.1%	1.03 [0.70, 1.50]
Total (95% CI)		**899**		**838**	**100.0%**	**1.30 [1.14, 1.49]**
Total events	346		250			

Heterogeneity: $Chi^2 = 1.93$, $df = 2$ ($P = 0.38$); $I^2 = 0\%$

Test for overall effect: $Z = 3.97$ ($P < 0.0001$)

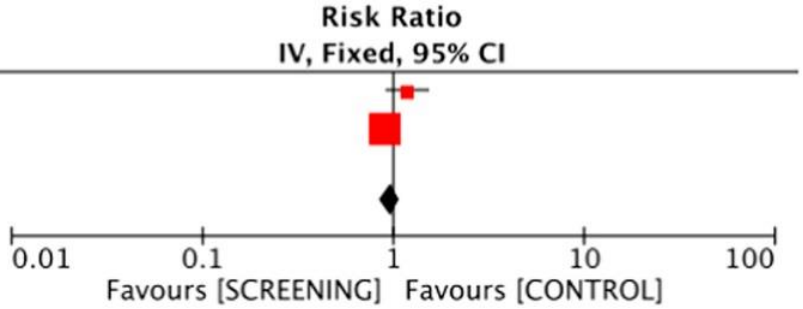


Disease specific mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
PLCO 2011	0.167	0.1357	24.3%	1.18 [0.91, 1.54]
UKCTOCS 2015	-0.1027	0.0769	75.7%	0.90 [0.78, 1.05]
Total (95% CI)			**100.0%**	**0.96 [0.85, 1.10]**

Heterogeneity: $Chi^2 = 2.99$, $df = 1$ ($P = 0.08$); $I^2 = 67\%$

Test for overall effect: $Z = 0.56$ ($P = 0.58$)



JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Ovarian Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jillian T. Henderson, PhD; Elizabeth M. Webber, MS; George F. Sawaya, MD

Study	False positive results
UKCTOCS CA125 ROCA	44.2%
TVUS	Not reported only for prevalence data
PLCO	9.6%
Surgical complication rate after false positive results	
3.07-15-09%	

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Ovarian Cancer

Updated Evidence Report and Systematic Review for the US

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Ovarian Cancer

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Ovarian Cancer

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF recommends against screening for ovarian cancer in asymptomatic women (D recommendation) (**Figure 1**).

This recommendation applies to asymptomatic women who are not known to have a high-risk hereditary cancer syndrome.

Rationale

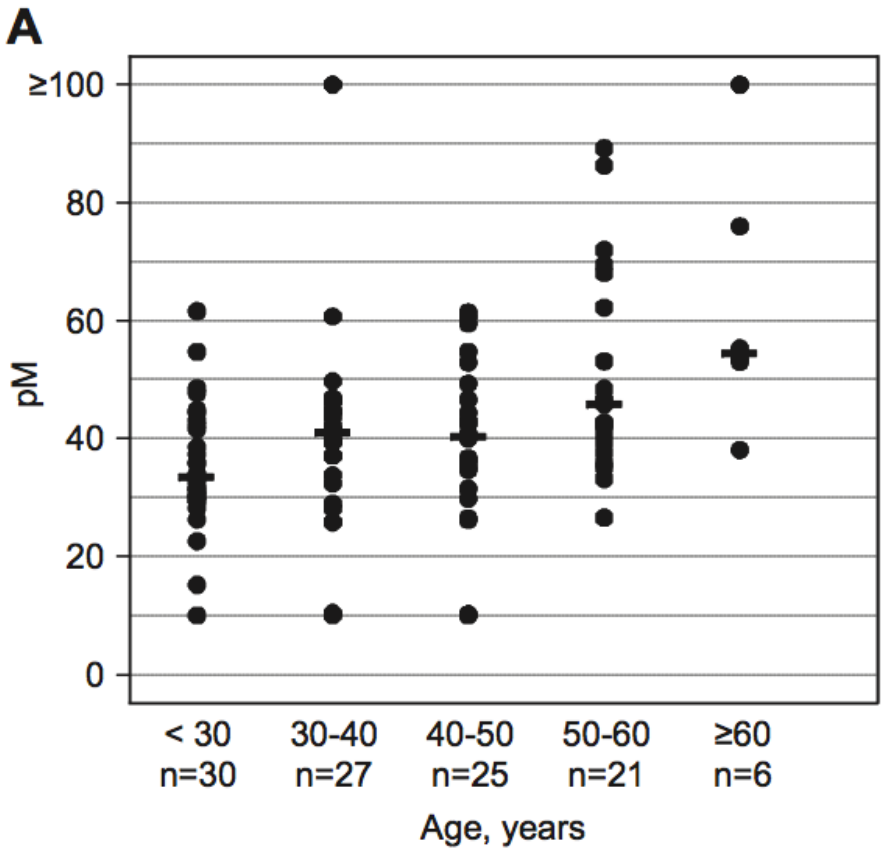
Importance

The age-adjusted incidence of ovarian cancer from 2010 to 2014 was 11.4 cases per 100 000 women per year.[1] Ovarian cancer is the fifth

Early detection

WDFC2 (*HE4*)

- first identified in the epithelium of the distal epididymis
- is frequently overexpressed in ovarian cancer patients, especially in serous and endometrioid EOC.
- could be overexpressed in endometrial and lung cancer
- higher HE4 levels are observed even in patients with renal failure or effusions
- HE4 belongs to the “four-disulfide core family“
- the function fo HE4 is unclear, there are suspected trypsin-inhibitor properties



HE4 Expression in healthy women

Linda Hertlein et al.
Clin Chem Lab Med 2012;50(12):2181–2188

Vergleich der ROC-AUC

Markerkombinationen	Benigne Erkrankungen vs. EOC	
	ROC-AUC (95% CI)	p-Wert AUC-ROC to CA125 + HE4
CA125 + HE4	**91.4% (86.7 - 96.0)**	**-**
CA125 + SMRP	86.3% (80.7 - 92.0)	0.0176
CA125 + CA72-4	86.2% (81.2 - 91.3)	0.0103
CA125 + Osteopontin	83.4% (77.5 - 89.4)	0.0019
CA125 + Activin	81.7% (75.2 - 88.3)	0.0004
CA125 + Inhibin	82.1% (75.6 - 88.6)	0.0027
CA125 + HE4 + SMRP	91.1% (86.3 - 95.9)	0.5325
CA125 + HE4 + CA72-4	91.4% (86.8 - 96.1)	0.7472
CA125 + HE4 + Osteopontin	91.5% (86.8 - 96.3)	0.5612
CA125 + HE4 + Activin	91.4% (86.7 - 96.1)	0.9805
CA125 + HE4 + Inhibin	91.7% (87.2 - 96.1)	0.7472
CA125 + HE4 + SMRP + CA72-4	91.2% (86.5 - 96.0)	0.6869
CA125 + HE4 + CA72-4 + SMRP +Osteo	91.4% (86.7 - 96.2)	0.8177

Moore et al, *Gynecologic Oncology*, 2008 (108) 402-408

Pilot Study: Marker Distribution

Ovarian Cancer	HE4 (+) CA125 (+)	HE4 (+) CA125 (-)	HE4 (-) CA125 (+)	HE4 (-) CA125 (-)
EOC (n=129)	71% (n=92)	9% (n=11)	11% (n=14)	9%(n=12)
Total	91%			9%

HE4 normal <140 pmol, CA125 < 35 U/ml

Brown et al, Differential expression of CA125 and a novel serum tumor marker HE4 in epithelial ovarian cancer ; ASCO 2007

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

BERLIN-ROMA

BERLINER-Study

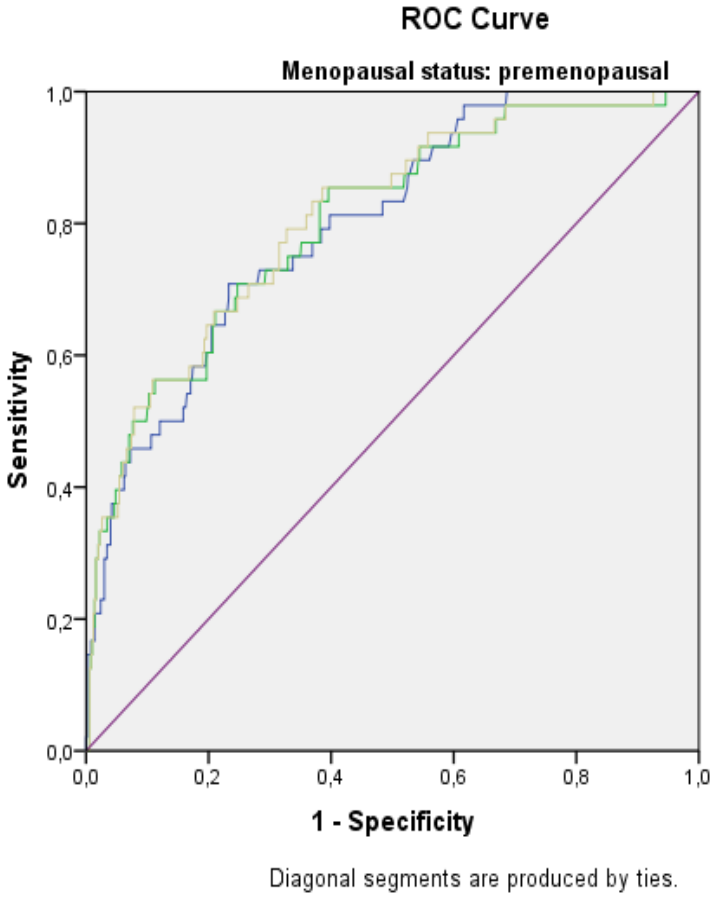
Sponsored by Roche Diagnostics

Patients' characteristics - diagnosis

Diagnose	n (%)
Benigne Tumoren	1014 (75,5%)
Endometriose	161 (12%)
Tubo-ovarielle Abszesse	19 (1,4%)
Dermoidzysten	91 (6,8%)
Zystadenome	221 (16,5%)
Zystadenofibrome	58 (4,3%)
Funktionelle Zysten	278 (20,7%)
Andere	212 (13,8%)
Ovarialkarzinom	126 (9,4%)
Seröse	93 (6,9%)
Endometrioide	19 (0,7%)
Andere	23 (1,7%)

Diagnose	n (%)
Borderline-Tumoren	49 (3,6%)
Seröse	32 (2,4%)
Muzinöse	17 (1,3%)
Andere	5 (0,5%)

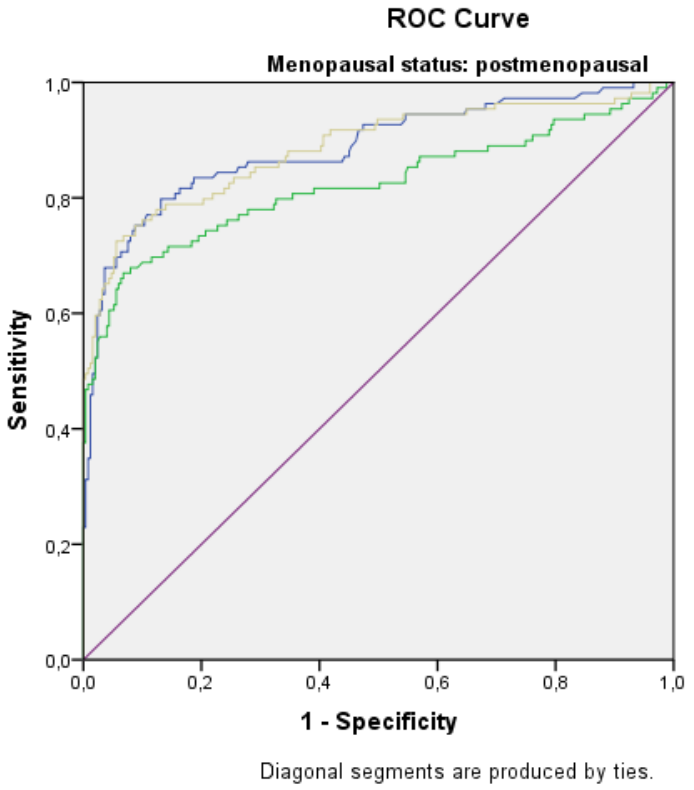
Results-premenopausal patients



Parameter	AUC	95%CI	P value
Ca125	0.799	0.738-0861	<0.001
HE4	0.802	0.736-0.869	<0.001
ROMA	0.809	0.744-0.874	<0.001

	Cut off	Se	Sp	PPV	NPV
Ca125	39.25	70.8	76.8	22.7	96.5
	21.5	81.3	60.1	16.3	97.1
	50.8	58.3	82.6	24.3	95.4
HE4	62.29	70.8	75.3	21.7	96.4
	53.18	85.4	60.4	17.2	97.7
	77.87	56.3	88.8	32.5	95.5
ROMA	9.1	85.4	61.4	17.6	97.8
	13.8	66.7	79.1	23.5	96.1
	21.4	52.1	92.2	39.1	95.2

Results- postmenopausal patients



Parameter	AUC	95%CI	P value
Ca125	0.886	0.844-0.928	<0.001
HE4	0.822	0.765-0.878	<0.001
ROMA	0.885	0.842-0.929	<0.001

	Cut off	Se	Sp	PPV	NPV
Ca125	30.1	80.2	86.9	73.8	90.5
	91.95	68.1	96.4	89.8	86.7
	20.25	87.1	72.1	59.1	92.3
HE4	110.1	65.8	93.2	81.5	85.7
	80.04	73.7	79.3	61.8	86.9
	61.2	81.6	60.2	48.2	87.8
ROMA	41	71.9	94.4	85.4	88.1
	18	84.2	74.5	60.0	91.2

Multivariate analysis - premenopausal

Parameters	P Value	OR	95% Confidence Intervall
History of cancer	<0.001	16.345	4.112-64.966
CA125 (log)	<0.001	1.925	1.377-2.690
HE4 (log)	0.015	1.823	1.124-2.958
Diameter papillary structure			
5-10 mm	0.021	4.373	1.252-15.277
>3 mm	<0.001	21.732	8.338-56.639
Ascites	<0.001	14.284	3.265-62.491

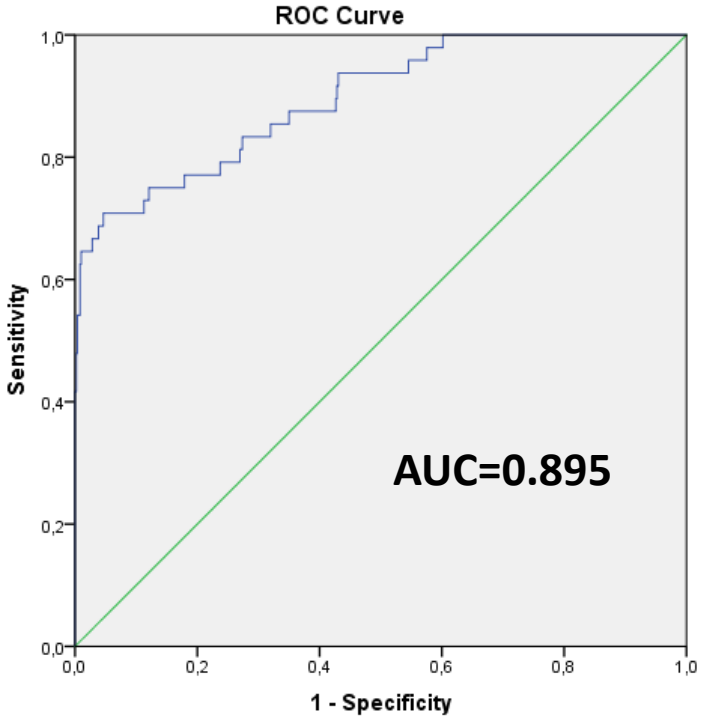
New Risk model – premenopausal patients

- stepwise logistic regression

•PreM=-8.423 + 2.794* (History of cancer) + (0.655*LN(CA125)) + (0.601*LN(HE4)) + 1.475* (ps_size 5-10 mm) + 3.079* (ps_size >3 mm) + (2.659*ascites)

BERLIN Score = exp(PreM) / [1 + exp(PreM)]*100

BERLIN score - premenopausal patients



Cut-off value	Sensitivity	Specificity	PPV	NPV
23.6	70.8	95.4	59.6	97.1
5.045	77.1	82.1	29.4	97.4
3.137	83.3	72.6	22.7	97.8

Multivariate analysis - postmenopausal

Parameters	P Value	OR	95% Confidence Intervall
CA125log	<0.001	2.027	1.401-2.933
HE4log	0.027	2.006	1.083-3.717
ps_number more than 3	0.001	12.689	2.718-59.247
malignancy_assessment_examinator	<0.001	4.414	1.971-9.888

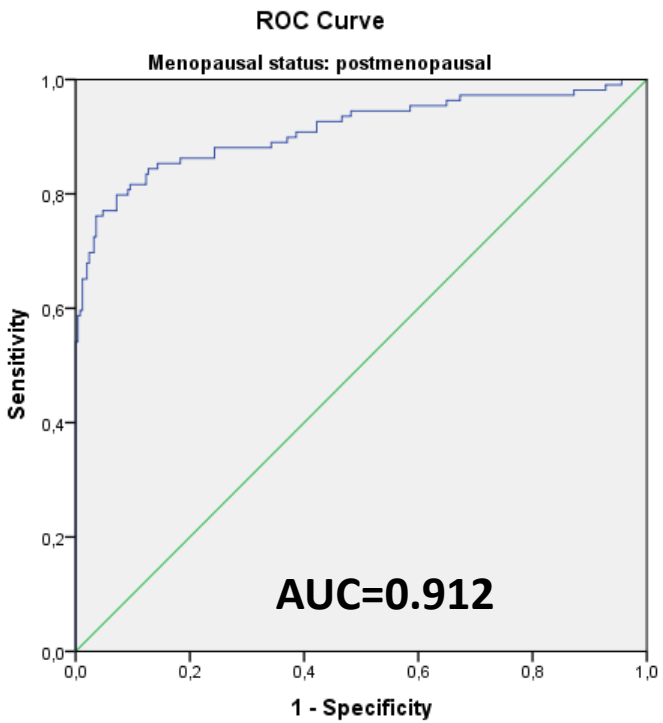
New Risk Model postmenopausal

- stepwise logistic regression

- PostM=-7.310 + (0.707*LN(CA125)) + (0.696*LN(HE4)) + (2.541*ps_number ≥3) + (1.485*malignancy_assessment_yes)

BERLIN Score = exp(PostM) / [1 + exp(PostM)]*100

Berlin Score postmenopausal



Cut-off value	Sensitivity	Specificity	PPV	NPV
31.4	79.8	92.8	82.9	91.4
21.6	84.4	87.3	74.2	92.8
11.9	88.1	88.1	75.7	93.6

Conclusions

- CA125 performs better than HE4 and ROMA in postmenopausal patients.
- HE4 slightly improved the sensitivity and specificity of CA125 in premenopausal patients
- Data generated by ultrasound improved the sensitivity and specificity of HE4 and Ca125

Ultrasound

Risk of ovarian malignancy index (RMI)

Table 1. Calculating the risk of malignancy index (RMI); these are modifications of the original RMI using modified scores

RMI = ***U*** x ***M*** x ***CA125***

U = 0 (for ultrasound score of 0); ***U*** = 1 (for ultrasound score of 1); ***U*** = 3 (for ultrasound score of 2–5)
Ultrasound scans are scored one point for each of the following characteristics: multilocular cyst; evidence of solid areas; evidence of metastases; presence of ascites; bilateral lesions.

M = 3 for all postmenopausal women dealt with by this guideline

CA125 is serum CA125 measurement in u/ml

Table 2. An example of a protocol for triaging women using the risk of malignancy index (RMI); data from validation of RMI by Prys Davies *et al.*[16]

Risk	RMI	Women (%)	Risk of cancer (%)
Low	< 25	40	< 3
Moderate	25–250	30	20
High	> 250	30	75

The International Ovarian Tumour Analysis (IOTA) collaboration

- encourage the development of better indices
- standardising ultrasound reporting across research groups
- and prospectively collecting a database of features observed

Morphologic Classification (n=1066)

Type of tumor	N	Malign.	%
1.Unilocular cyst	313	2	**0.6**
2.Unilocular solid	132	44	**33**
3.Multilocular cyst	196	20	**10**
4.Multilocular solid	284	116	**41**
5.Solid tumor	136	84	**62**

(IOTA, JCO 2005, 23, 8794-8801)

Risk factors for malignancy (multivariate analysis)

1. Age (+3% risk per year)
2. personal history of ovarian cancer (Odds 4.95)
3. Max diameter of lesion (+0.8% per mm)
4. Max diameter of solid component (+5% per mm)
5. Presence of ascites (Odds 4.72)
6. Presence of blood flow within papillary projection (Odds 3.23)
7. Irregular internal cyst walls (Odds 3.13)
8. Presence of a purely solid tumour (Odds 2.53)
9. Color score (Odds 1.64 for every one unit increase)

(JCO 2005, 23, 8794-8801)

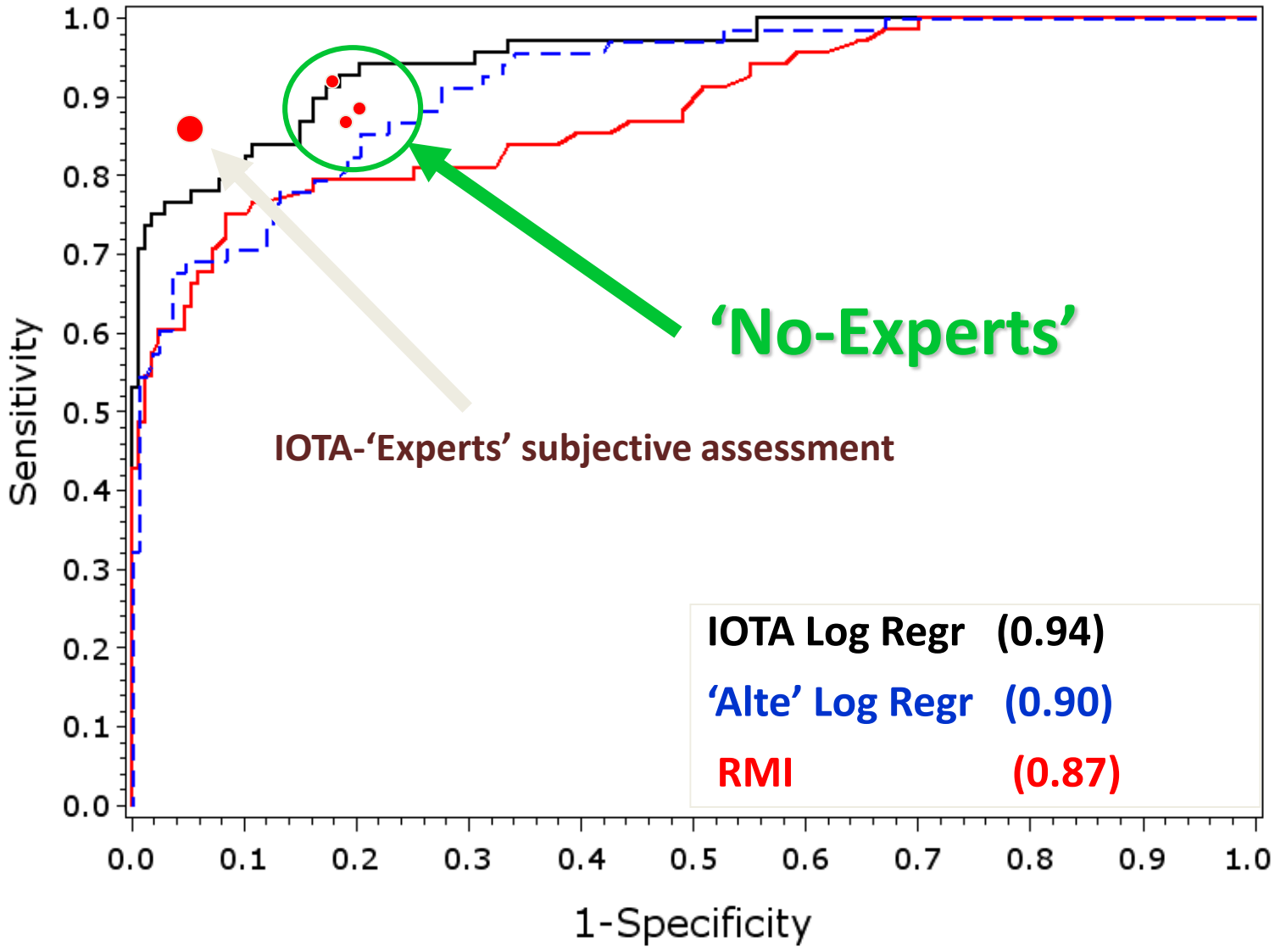
Factors that reduce the risk

(multivariate analysis)

1. Presence of acoustic shadows (Odds 0.095)
2. Current hormonal therapy (Odds 0.369)
3. Presence of pain during the examination (Odds 0.424)

(JCO 2005, 23, 8794-8801)

Comparison of tests (n=312)



Dualistic Model of Ovarian Cancer

Type I ovarian cancer

Low-grade serous, low-grade endometrioid, clear cell, mucinous

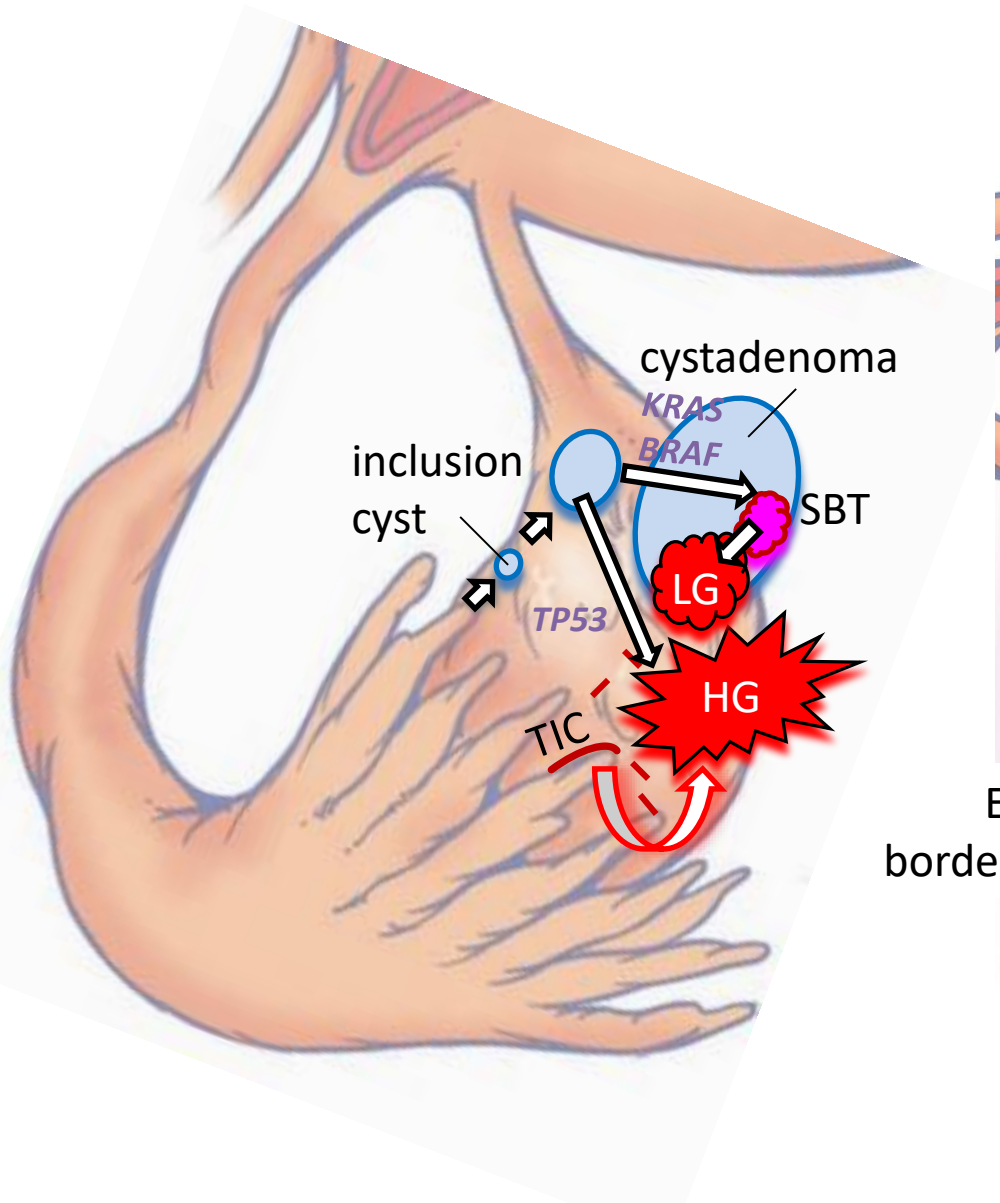
- Younger patients
- ⬇ chrom instability (CIN)
- *KRAS, BRAF, PIK3CA, ARID1A, CTNNB1, PTEN* mutations
- Borderline tumor
- Often low-stage
- Indolent clinical course
- Better overall survival

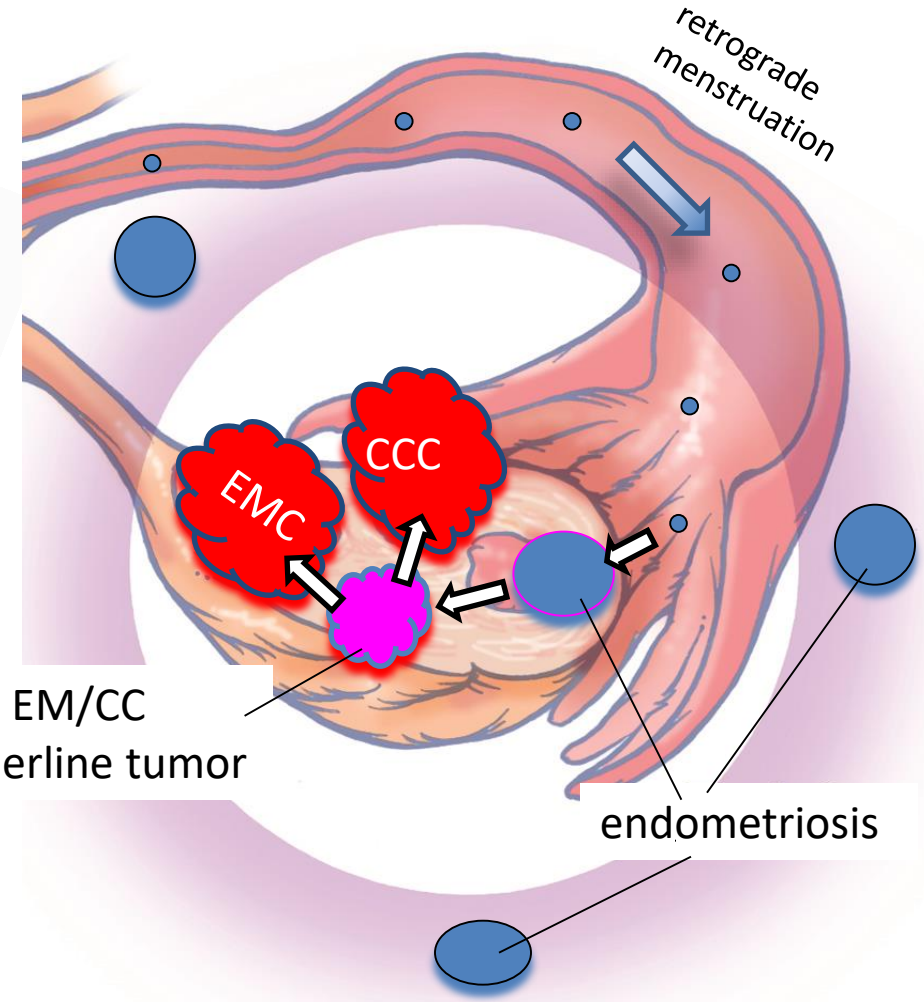
Type II ovarian cancer

High-grade serous, poorly differentiated, carcinosarcoma

- Older patients
- ⬆ high CIN *CCNE1* amplification
- *TP53, BRCA1/2* mutation
- "Imported" from FT
- Always high-stage
- Rapid progression
- Poor overall survival

Cell of origin in ovarian cancer subtypes





AACR American Association for Cancer Research

Clinical Cancer Research

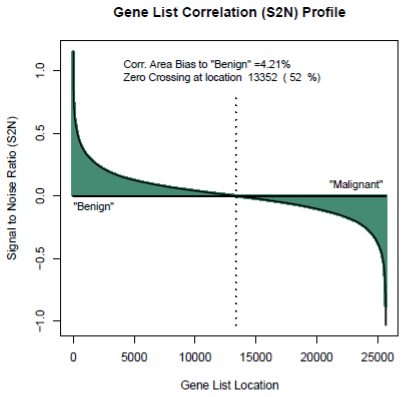
Creation of a human Secretome: Novel Composite Library of Human Secreted Proteins: Validation using Ovarian Cancer Gene Expression Data and Virtual Secretome Array

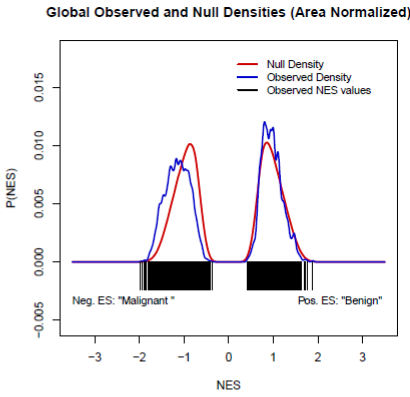
Vinod Vathipadiekal, Xin Victoria Wang, Wei Wei, et al.

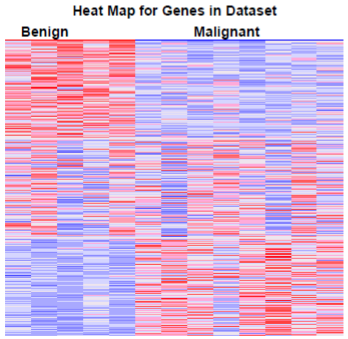
Clin Cancer Res Published OnlineFirst May 5, 2015.

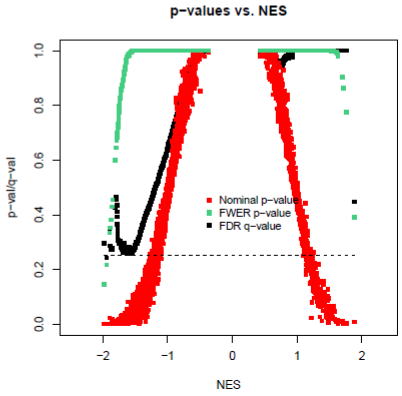
In Silico data analysis from *GSE29156*

Malignant versus benign Epithelium

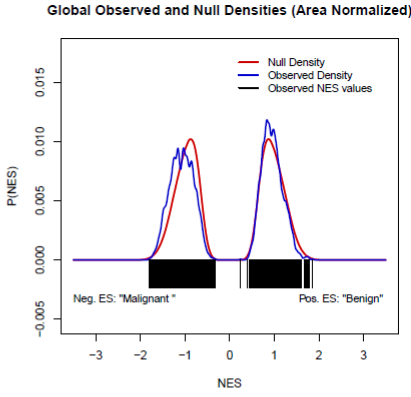


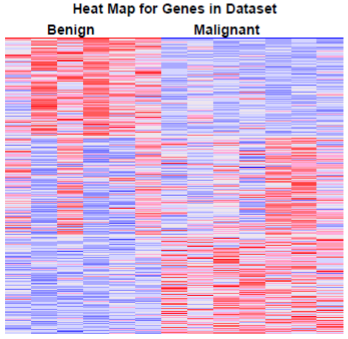


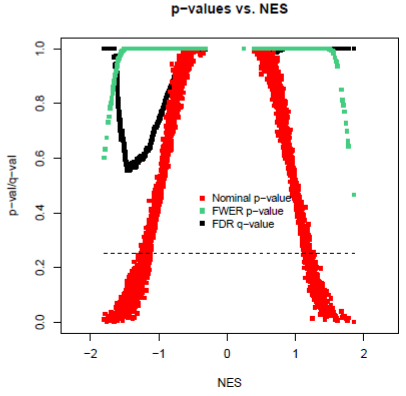




Malignant versus benign Stroma



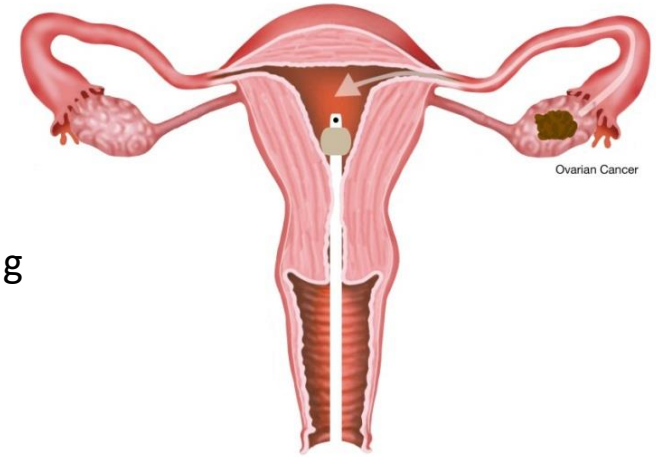


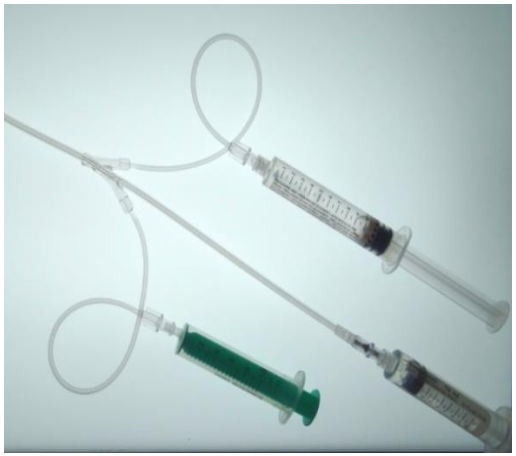


Vathipadiekal V et al., Clin Cancer Res. 2015 Nov 1;21(21):4960-9

Uteruslavage

.....Comunicating compartments





Fallopian tube – stem cells can build *in vitro* Organoid

nature COMMUNICATIONS

ARTICLE

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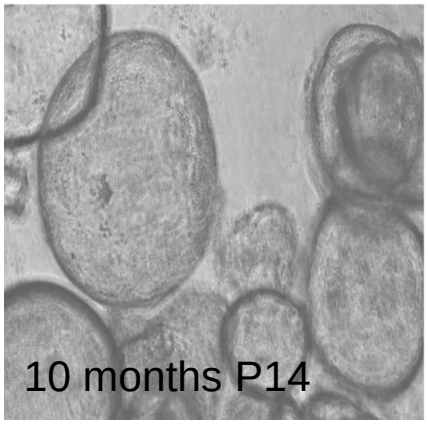
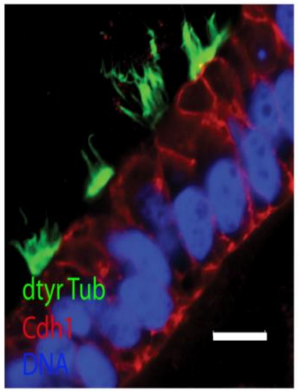
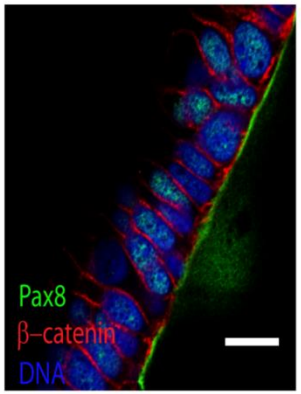
The Notch and Wnt pathways regulate stemness and differentiation in human fallopian tube organoids

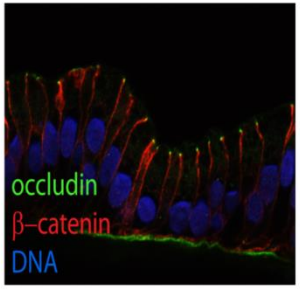
Mirjana Kessler[1], Karen Hoffmann[1], Volker Brinkmann[2], Oliver Thieck[1], Susan Jackisch[1], Benjamin Toelle[1], Hilmar Berger[1], Hans-Joachim Mollenkopf[3], Mandy Mangler[4], Jalid Sehouli[5], Christina Fotopoulou[5,†] & Thomas F. Meyer[1]

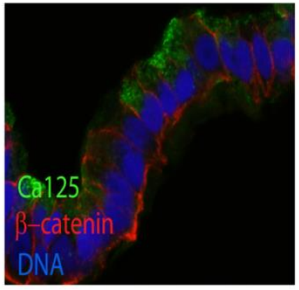
- Long time culture >1 Jahr
- NOTCH Signaling is mandatory for cell differentating
- Together with WNT responsible for stemness regulation











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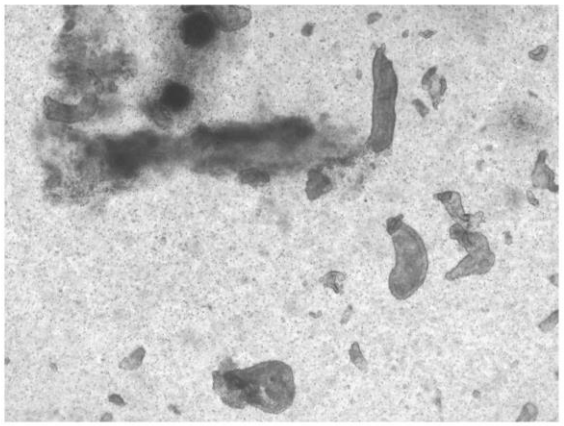
Lavage BRCA1 PR

p0



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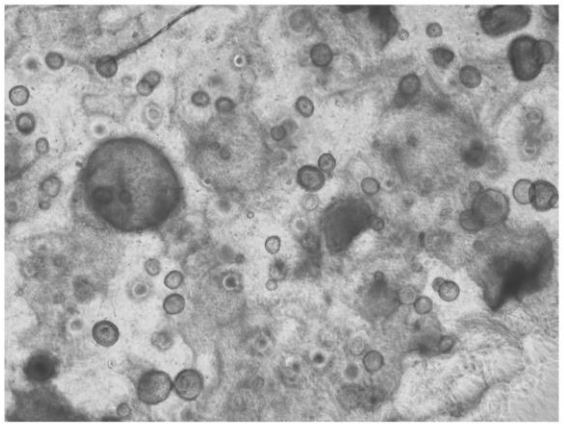

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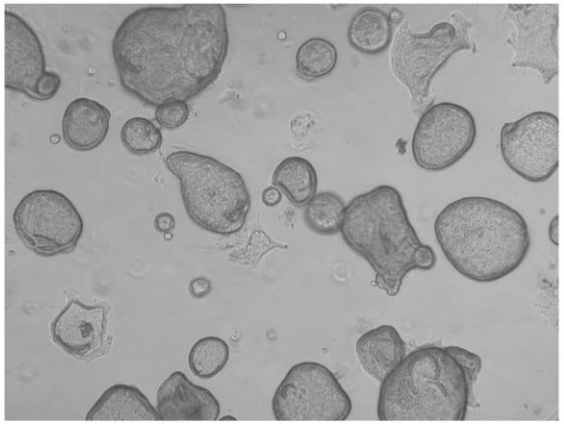
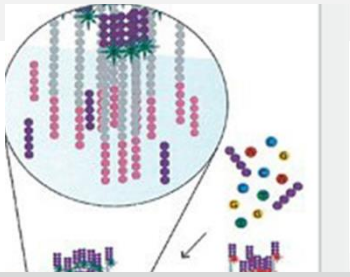
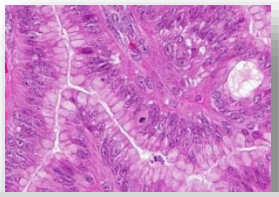


23/11/16

Different types of ovarian cancer





morphologically distinct
ups

Ultrasound + Biomarker

ARID1A

PTEN
PP2R1A

TP53

Mucinous

ARID1A
PIK3CA

Endometrioid

Clear cell

Biomarker (velocı

Ultrasound

High-grade serous

Primary ovarian carcinoma

KRAS/BRAF/ERRB2