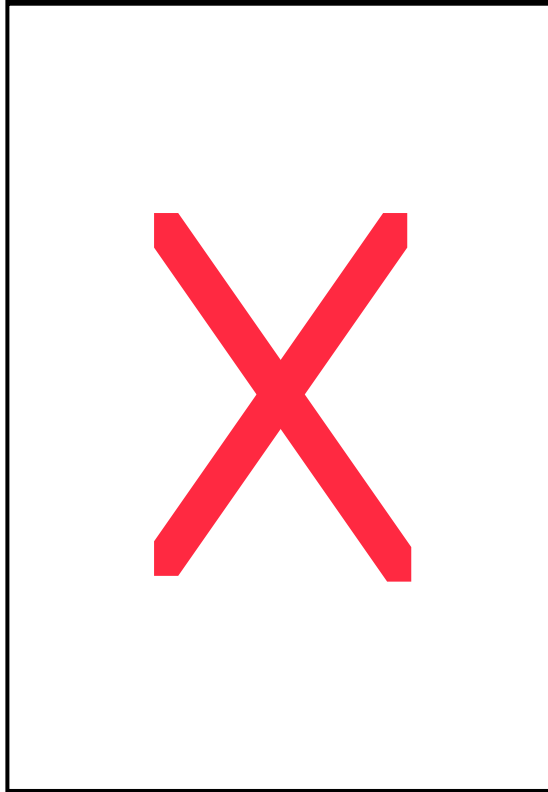




Early Detection of Ovarian and Endometrial Cancers



Lucy Gilbert MD, MSc, FRCOG

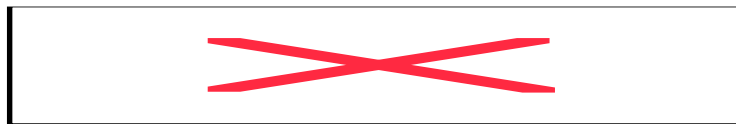
Professor

Department of Obstetrics &
Gynecology

Department of Oncology
McGill University

Director

Gynecologic Cancer Service
McGill University Health Centre



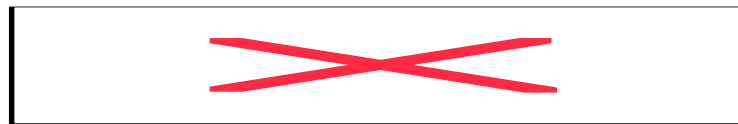


Learning Objectives



Endometrial / Ovarian cancer

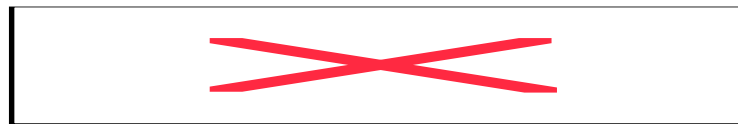
1. Recognize the symptoms
2. Be aware of the appropriate investigations you can do
3. Recognize when to refer and to who





Conflict of Interest and Disclosures

- Conflict of interests
 - None
- Disclosures
 - Nil Relevant



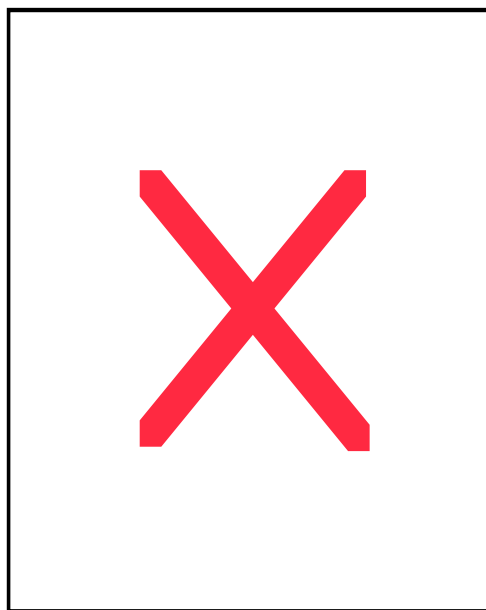
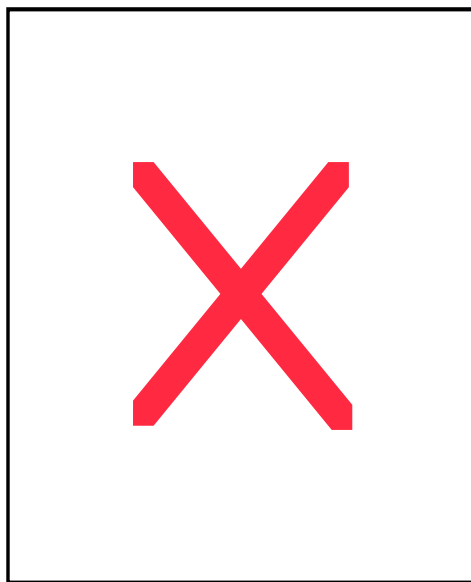


Disclosures

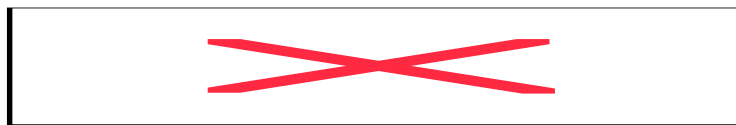


Disclosures

- Research supported by
 - CIHR, NCI, DOD
 - Philanthropy,
 - Industry AZ, Pfizer, Tessaro, Immunogen, Pfizer



Dr John Clarke
New England,
1664



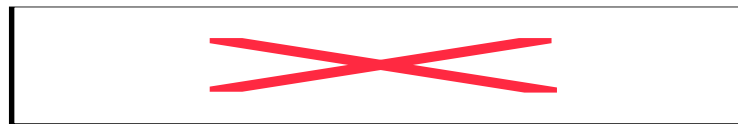


Disclosures



Pathologically obsessed with

- Early Diagnosis





Impact of Early Diagnosis

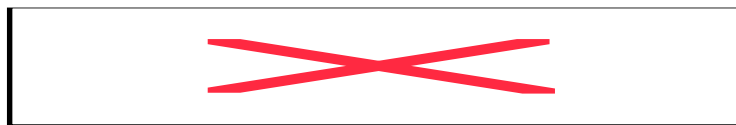


Uterine Cancer	
FIGO Stage	5-Year Survival
I	86%
II	81%
III A	67%
IIIC	56%
IV	21%

Ovarian Cancer	
FIGO Stage	5-Year Survival
I	85%
II	66%
III A	47%
IIIC	32%
IV	19%

From SEER database
 Patients treated 1988-2006
 UpToDate

FIGO, From Heintz 2006
 Patients treated 1999-2001



In North America

Ovarian and Endometrial cancer

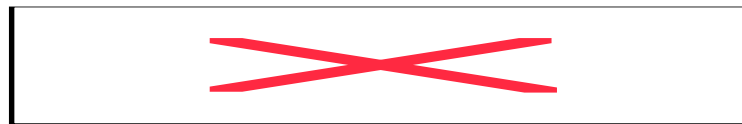
- Together 86% of gynecologic cancers
- Of ALL Cancers affecting women within top 4
 - Incidence
 - Death
 - Health Care expenditure

Ovarian Cancer

- Escalating treatment costs but cure rates unchanged in three decades

Endometrial cancer

- Incidence is increasing
- Death rates increasing

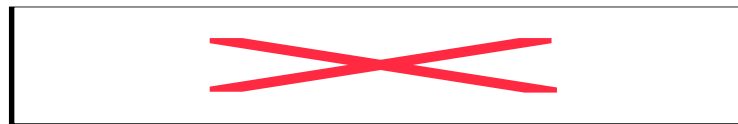




Case I JT



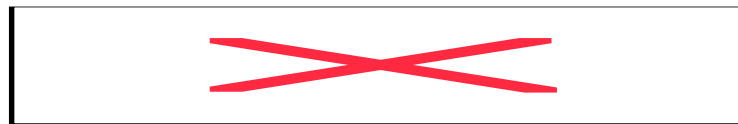
- 56 year old
 - Nulliparous
 - BMI 43
 - Hypertension
 - Type II diabetes
 - Low dose aspirin
- Complains of fatigue
 - HB 96 g/dL
 - She says she still has her periods
 - Periods never really stopped but recently they are heavier
 - her mother too had a very late menopause
 - She would like treatment to stop the periods





Management?

- A. Stop low dose aspirin and assess after 6 weeks
- B. Start low dose oral contraceptive pill
- C. Start oral progestins – provera
- D. Arrange endometrial biopsy
- E. Pap smear

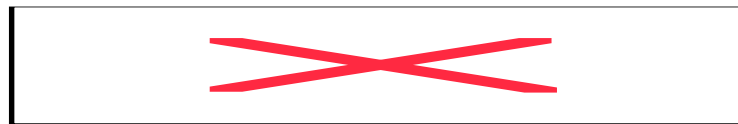




What is the likely diagnosis?



- a. Late menopause (like her mother)
- b. Endometrial Hyperplasia
- c. Endometrial cancer
- d. Bleeding provoked by low dose Aspirin
- e. a / d
- f. b / c

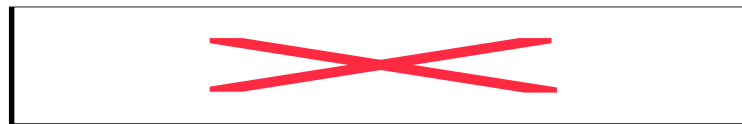




What are the risk factor in this pt

56 year old, nulliparous, BMI 43, on antihypertensive, diabetic, low dose aspirin

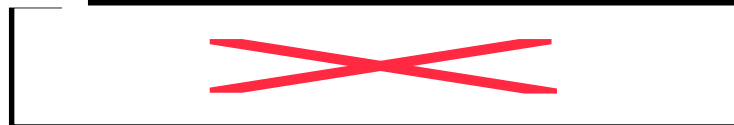
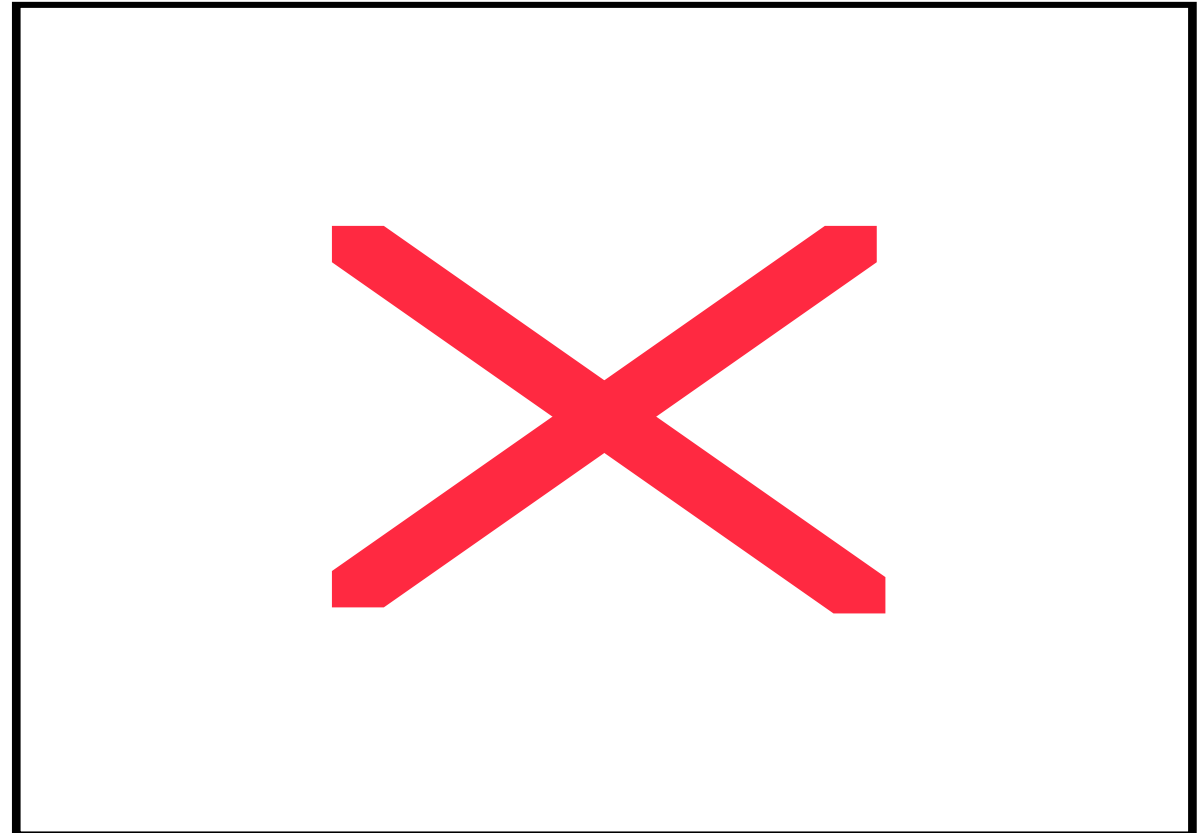
- Age
- Post-menopausal
- Nulliparous
- Obesity
- Hypertensive
- Diabetic





Uterine Cancer

- Uterine Cancer also called Cancer -Corpus
 - Is essentially Endometrial cancer
 - As Sarcoma is rare

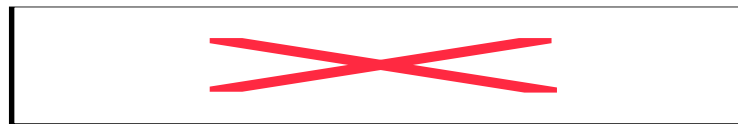




You should consider the possibility of endometrial cancer in the context of

- A. Post menopausal bleeding
- B. Irregular bleeding after 45
- C. Thickened endometrium in a postmenopausal woman
- D. A / C
- E. All of the above

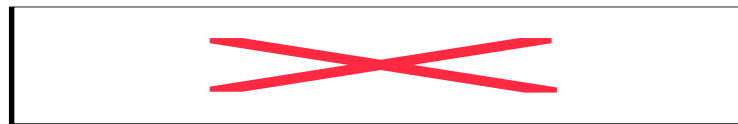
If obese, low parity in younger women





Risk factors for endometrial cancer

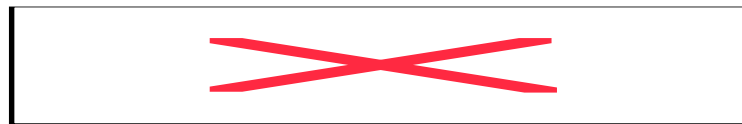
- A. Nulliparity / low parity
- B. Obesity
- C. Tamoxifen
- D. Family history of young colon cancer
- E. A, B, C
- F. All of the above





The best and most cost effective investigation to establish a diagnosis of endometrial cancer is

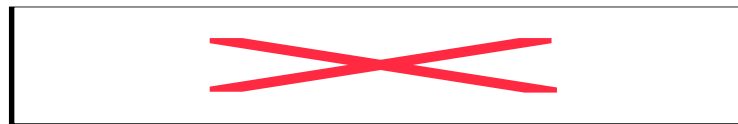
- a. Transvaginal ultrasound
- b. Liquid based cytology – Thin Prep
- c. Endometrial biopsy
- d. CA125
- e. A and D
- f. All of the above





Role of Imaging for Gynecologic Disease

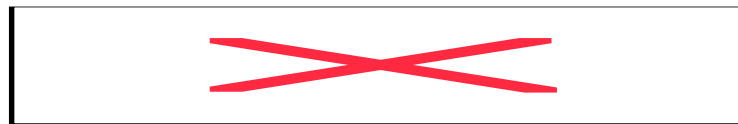
- Transvaginal ultrasound scan
 - Cheap, minimal risks
 - v good to view uterus, endometrium, ovaries
- Transabdominal Ultrasound Scan
 - poor resolution of gynecologic organs
- CT scan
 - good for chest, abdomen
 - so useful to do chest, abdo pelvis if you are searching
 - poor resolution of gynecologic organs
- MRI of the pelvis
 - v good for gynecologic organs
 - best resolution of all imaging
 - Long time –so reserve for when detail needed





Role of Imaging for Gynecologic Disease

- Transvaginal ultrasound scan
 - Cheap, minimal risks, v good to view uterus, endometrium, ovaries
- For Post menopausal bleeding
- Good as the first step, reassuring
 - If endometrium thin $<4\text{mm}$, no other abnormalities
 - If Pap smear normal
 - But if bleeding persists biopsy warranted

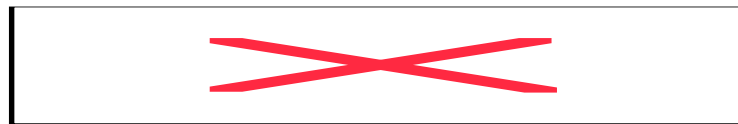




Key messages

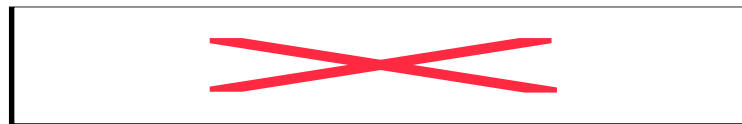


- Uterine Cancer = Endometrial Cancer
 - Most common gynecologic cancer
 - 4th Most common cancer in Women
 - Lifetime risk 1/32
 - ANY change in bleeding –heavy or irregular in perimenopausal women warrants investigation
 - Biopsy best
 - Best treatment
 - Surgical staging, Hysterectomy, BSO, LND



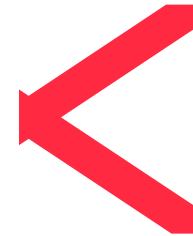
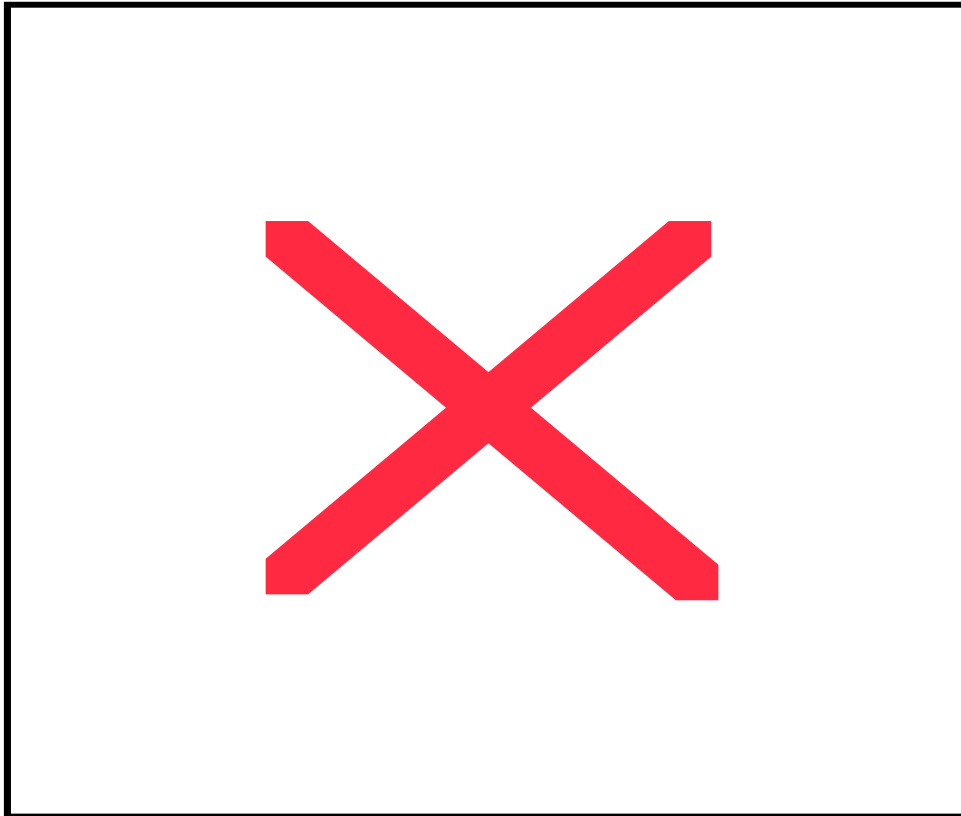
Endometrial Cancer

- Most Endometrial cancer deaths are caused by high grade subtypes -HGSC
- These cancer cells exfoliate and spread while the primary cancer is small
- HG endometrial cancer can arise in a background of atrophic endometrium
- Very low threshold for biopsy

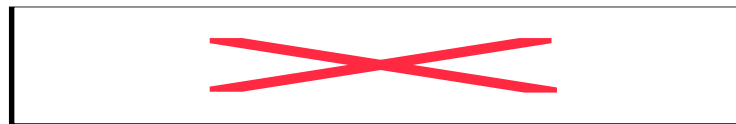




Role of PAP test?



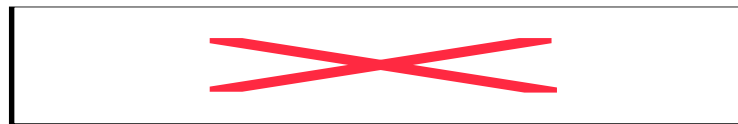
For the
diagnosis of
Precancer of
the cervix





Role of PAP test?

- NOT for CANCER of cervix, uterus, ovaries
- Invasive cancer of the cervix
 - pap test can be false negative
- Endometrial cancer
 - Pap test negative in 85%
- Ovarian cancer
 - Pap test negative >98%



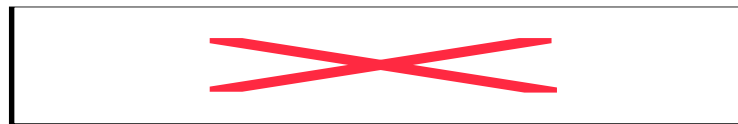


Case II AD



- 62 year old university lecturer
- has one daughter,
- non smoker
- no medical illness
- vague abdominal discomfort
- Started as a feeling of indigestion after a trip to Mexico 4 months ago
- getting progressively more persistent.
- Had routine colonoscopy 2 years ago – results normal.

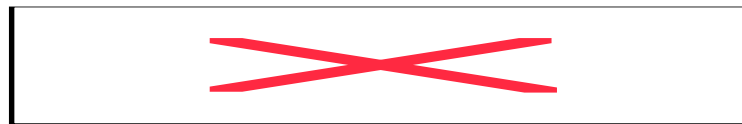
What do you recommend?





Ovarian Cancer is a heterogeneous disease

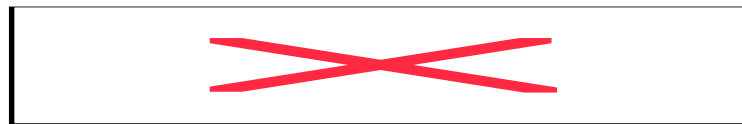
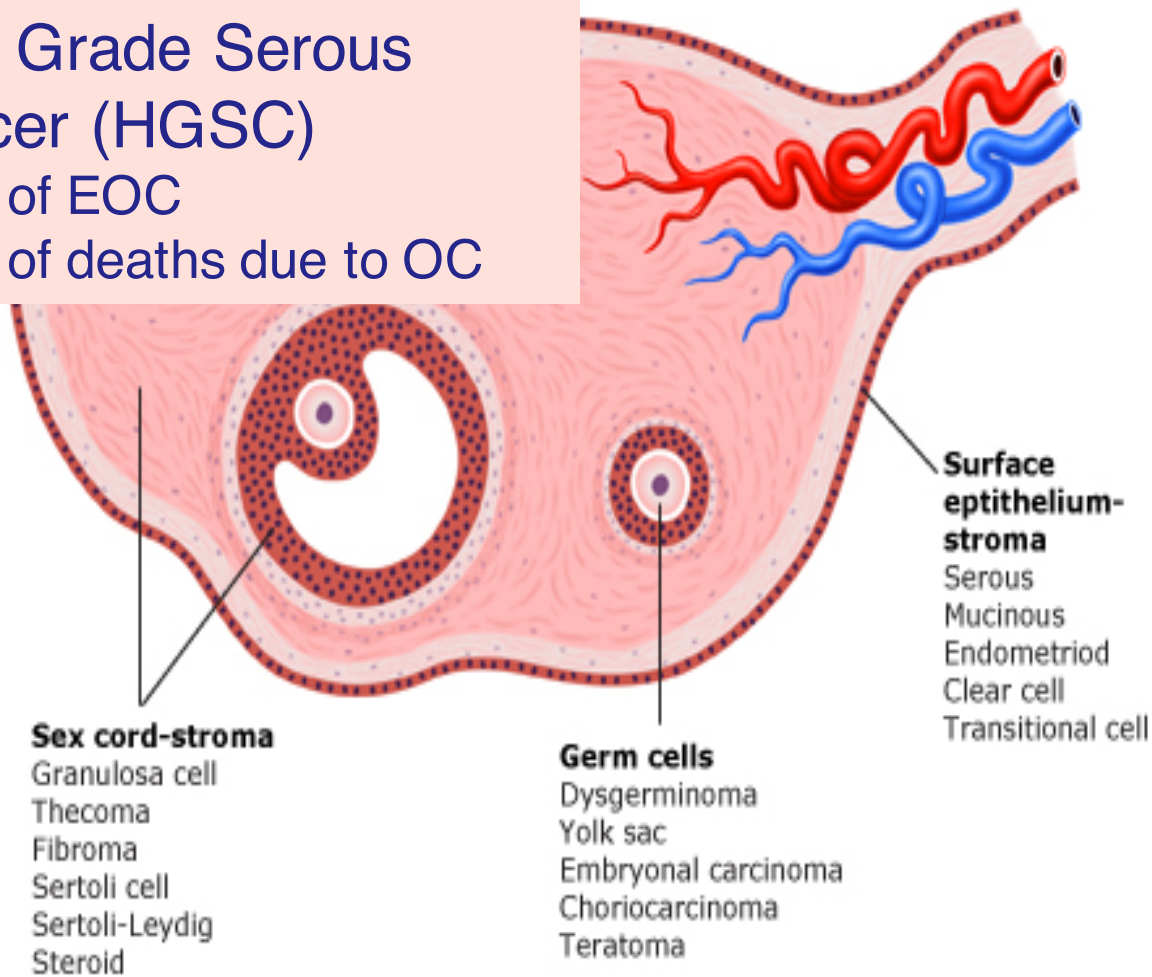
- The most common type is
 - High Grade Serous Cancer - HGSC
- Most of the deaths from OC are from HGSC
- 75% of HGSC starts in the fallopian tube

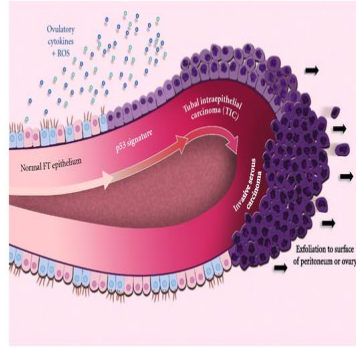
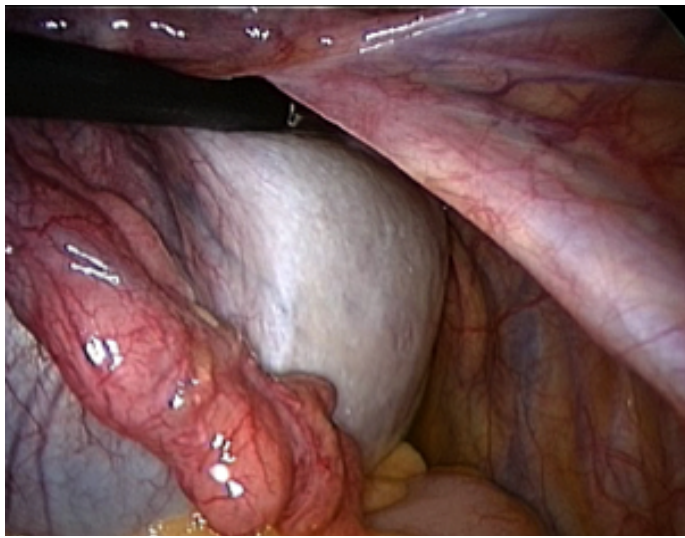


Ovarian Tumors -Origin

High Grade Serous Cancer (HGSC)

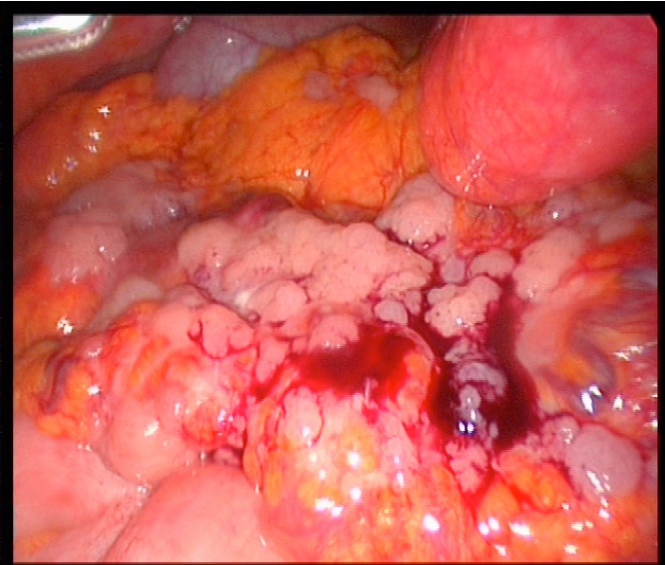
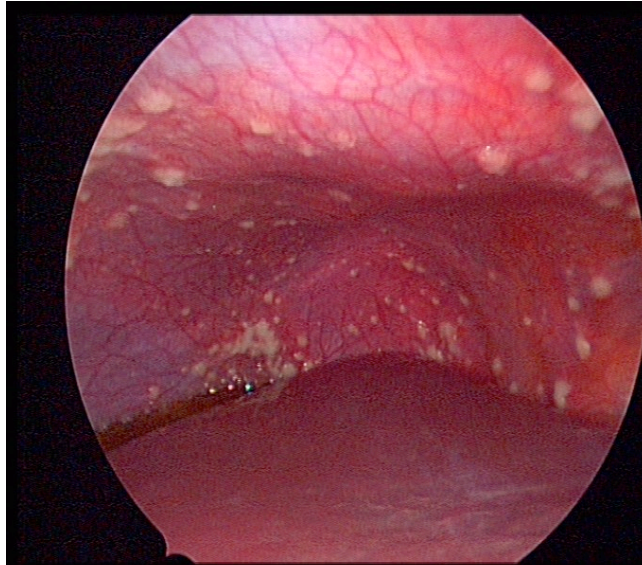
- 75% of EOC
- 90% of deaths due to OC





DOvE project

Diagnosing Ovarian cancer Early



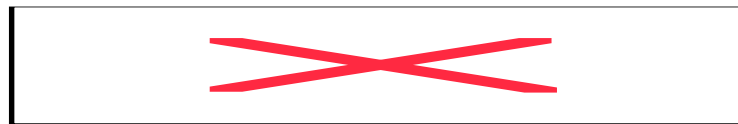
Gilbert et al, 2012
Lancet Oncology



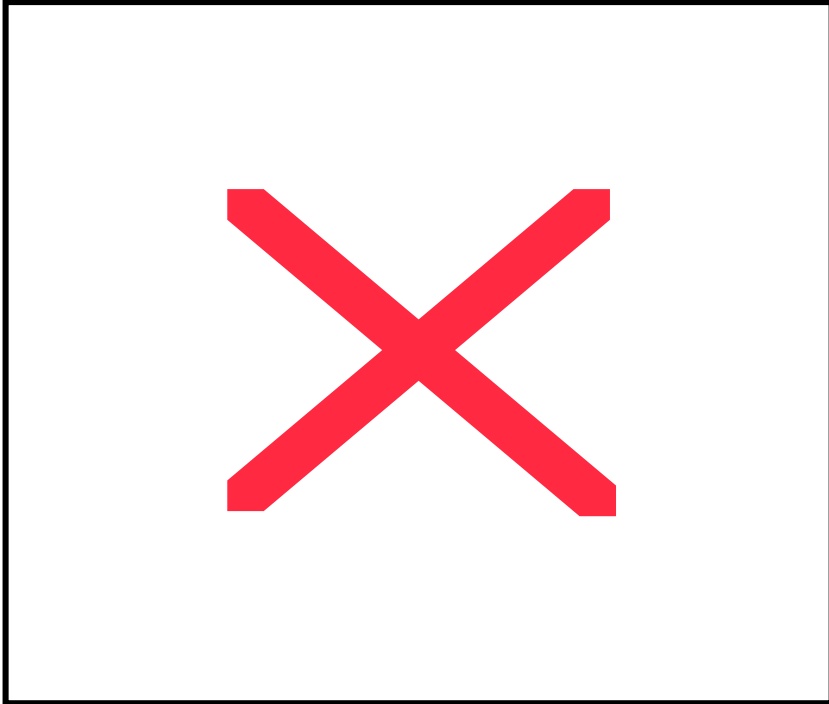
HGSC – of the Fallopian



- Spreads to the abdomen very early like snow flakes
- While the ovaries and tubes look normal to the naked eye and on imaging
- Already on its way to the paracolic gutter
- Undersurface of the diaphragm



High mortality because of Late diagnosis of HGSC



Stage I; <10% detected at this stage
outright cure with surgery

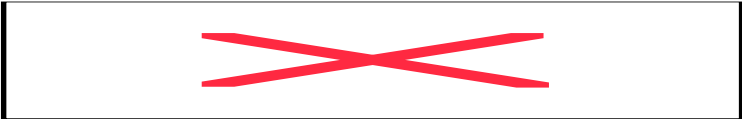
Stage II; < 10% detected at this stage

Stage III >50% diagnosed in this Stage, despite
radical surgery and toxic chemo 65% will die

Stage IV 29% diagnosed in this Stage, 90% will
die



Data for ovarian cancer from NIH SEER 18 2008-2014
Torre, 2018



Frequency of symptom categories in women with ovarian cancer

Type of symptom	Percent
Abdominal	77
Gastrointestinal	70
Pain	58
Constitutional	50
Urinary	34
Pelvic	26

Adapted from Goff BA, Mandel L, Muntz HG, Melancon CH. Cancer 2000; 89:2068.

UpToDate®

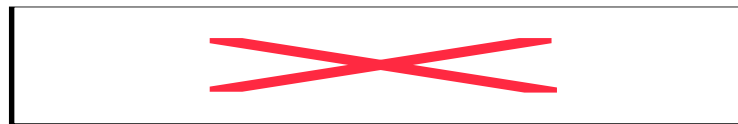




HGSC – of the Fallopian

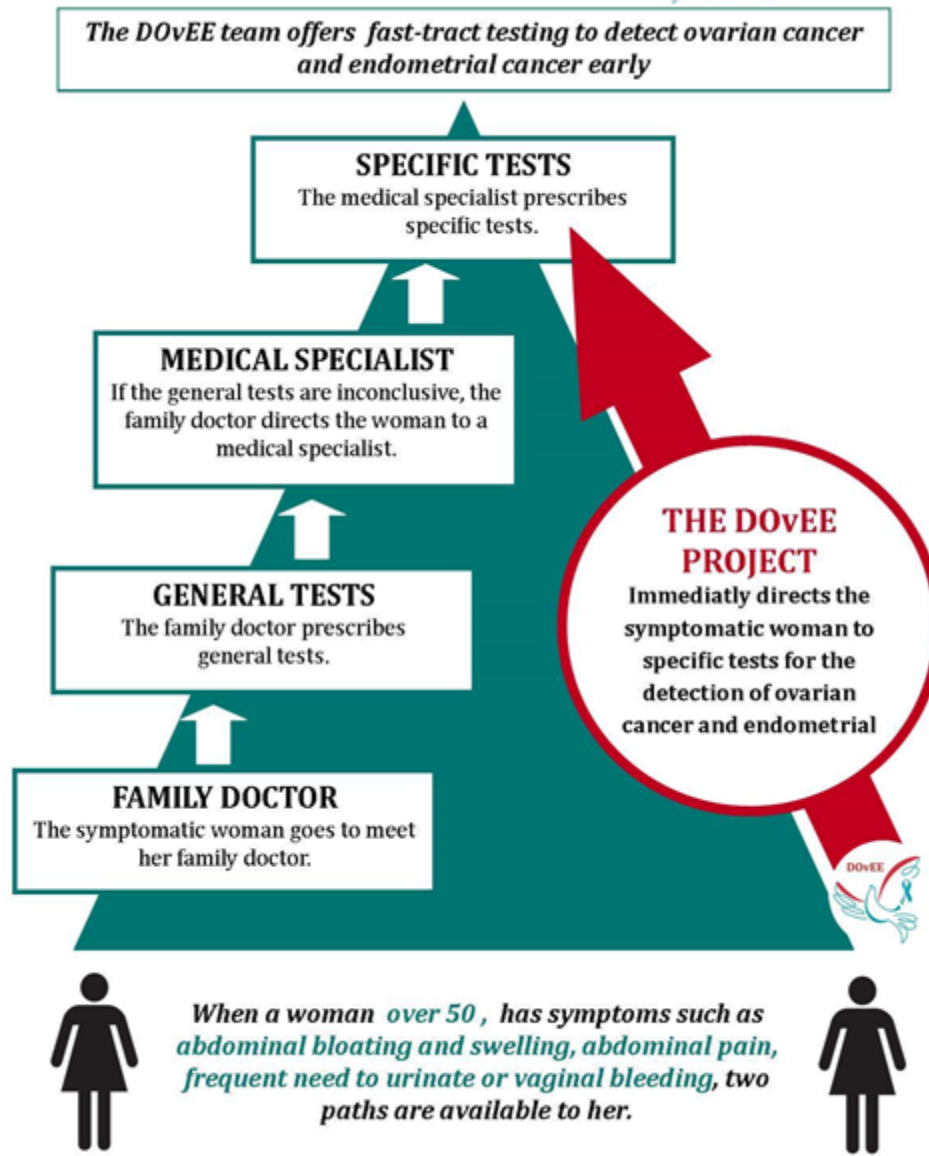


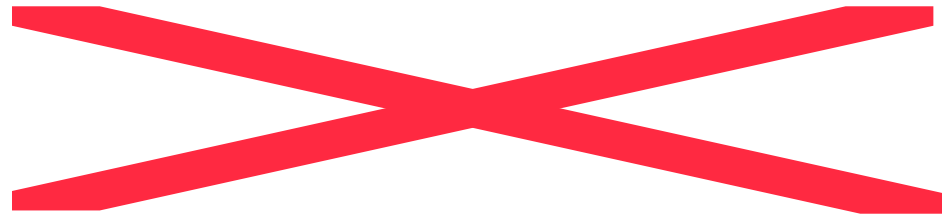
- CA125 and TVUS **NOT** recommended as screening test
 - Buys et al (PLCO Study) 2011
 - Jacobs et al (UKCTOCS Study) 2016
 - Grossman (USPSTF) 2018
- **Serial CA125 non-specific but may lead to diagnosis for the symptomatic patient with vague symptoms**
 - Better than TVUS



DOvEE

Detecting Ovarian Cancer early

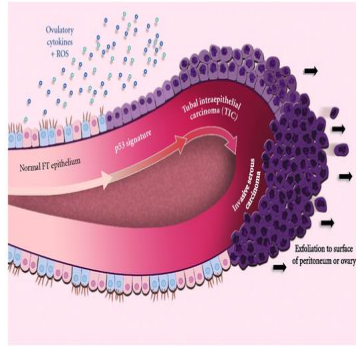
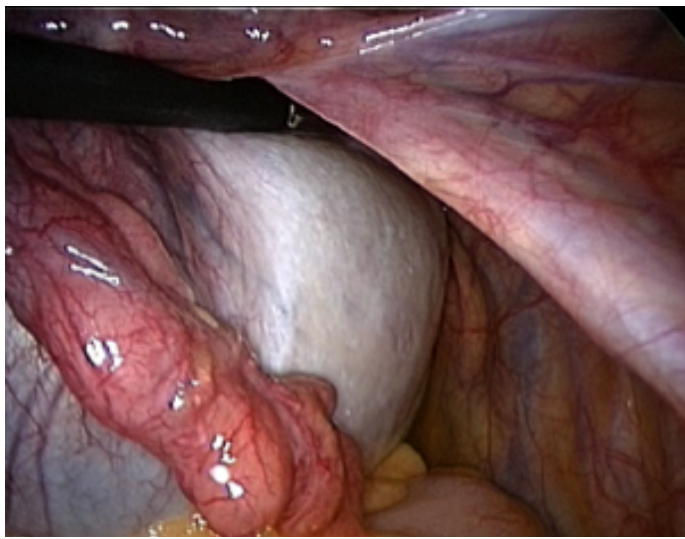




The Lancet Oncology, 2012

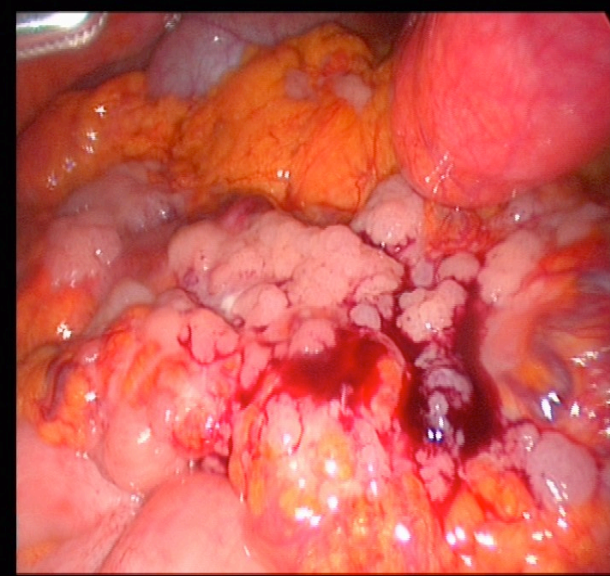
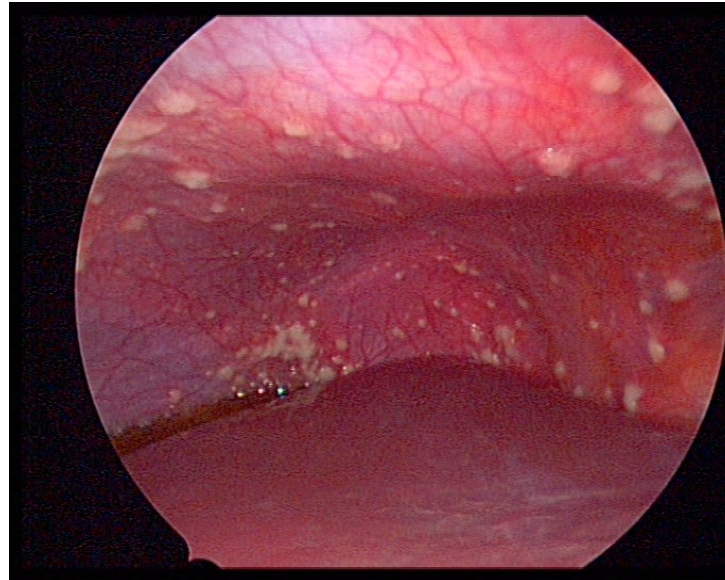
70% of HGSC Ovarian cancer did not originate in the ovary but in the Fallopian Tube

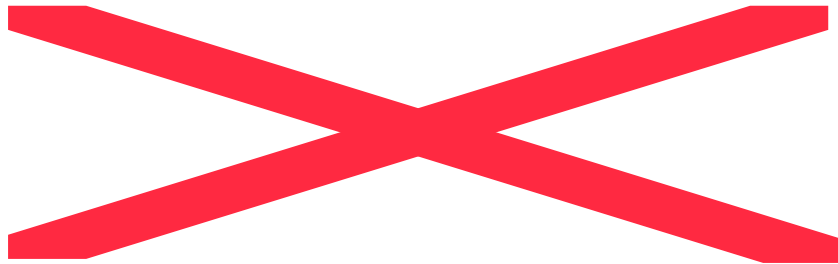
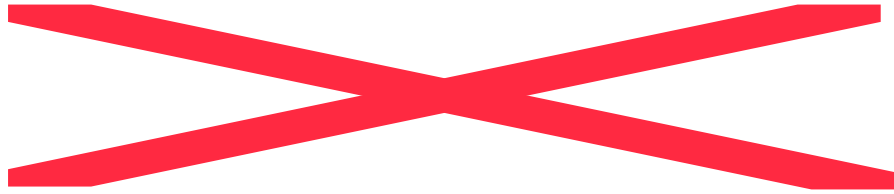




DOvE project
75% of
HGSC
started in the
fallopian
tube

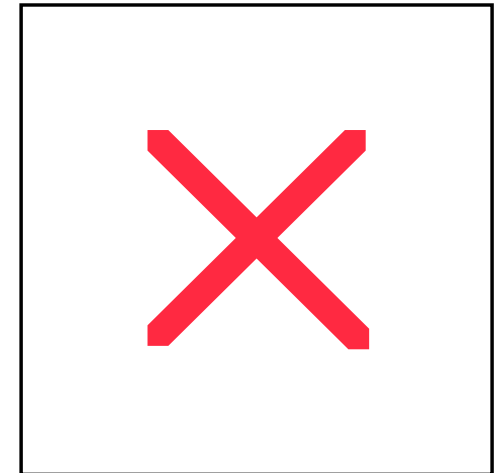
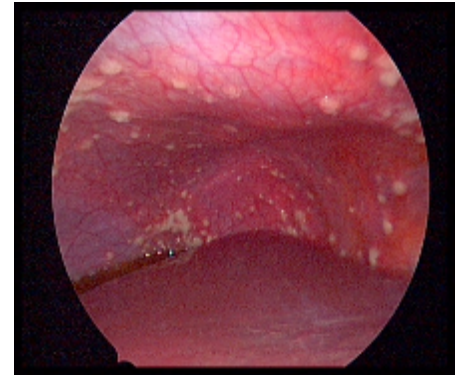
Gilbert et al, 2012
Lancet Oncology





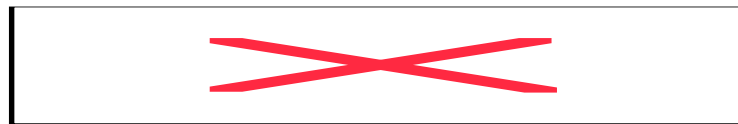
The Challenge:

- Early Cancer
 - No symptoms
 - cannot be seen on imaging
 - No early blood test
- So no screening for asymptomatic women
- Cancer cells exfoliate
- The 'cytology cervical Pap test' success story for cervical cancer



The Solution: The 'genomic uterine Pap

- Detect the first step in carcinogenesis
 - Somatic mutations





Cervical pap detection rate

Endometrial cancer 81% (95% CI, 77 to 85%)

Ovarian Cancer 33% (95% CI, 27 to 39%)

Intra uterine pap detection rate

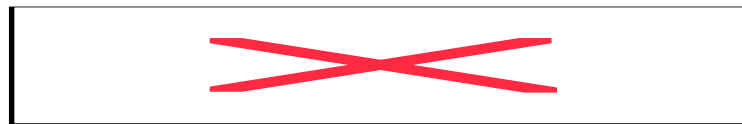
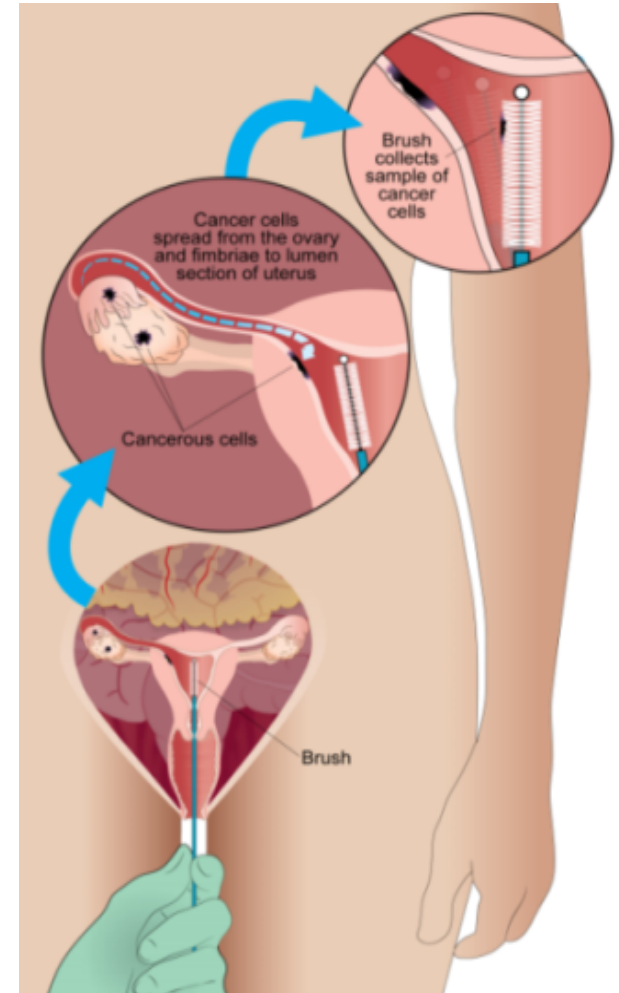
Endometrial cancer 93% (95% CI, 87 to 97%)

Ovarian Cancer 45% (95% CI, 31 to 60%)



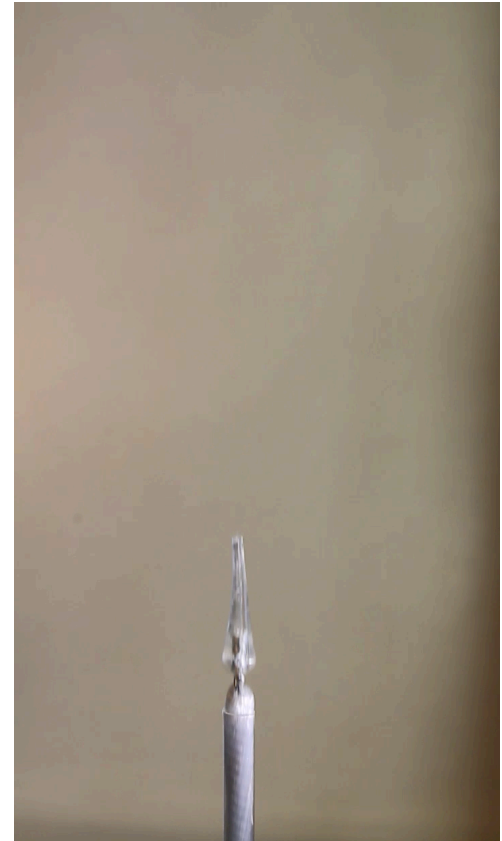
Genomic PAP test - DOvEEgene

- Intra uterine Pap
- Improved the gene panel
 - 23 genes implicated in sporadic and hereditary mutations in ovarian/ endometrial cancer
- NGS-based targeted sequencing assay (Haloplex^{HS})
- Identifies
 - Prevalent cancer – somatic mutations
 - Also germline mutations in so predisposition to Breast, Ovary and Colon cancer

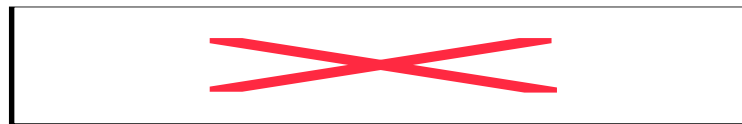


DOvEEgene– Endometrial sampler

- Designed for easy use in office
- Collects intrauterine fluid and dislodged cells



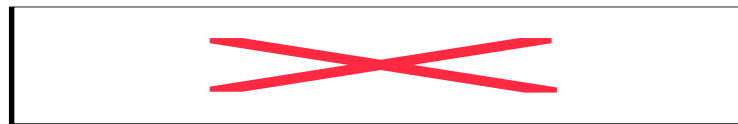
Phase III clinical trial starts early 2020





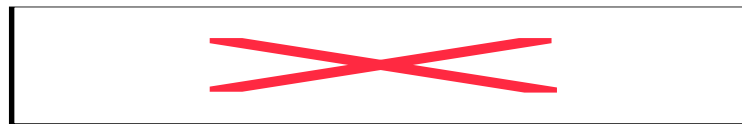
Key points

1. Deaths from OC and endometrial cancer – third most common cause of death in Canadian women
2. Irregular Bleeding in women over 45 must be investigated by endometrial biopsy
3. Persistent Vulval itching –please examine may be cancer
4. The majority of cancer of the cervix in Canada in women not screened or long period of time
5. Ovarian Cancer -gynecologic symptoms rare -mimics other diseases CA125 useful for symptomatic patients



Key Take away points

- Ovarian Cancer -Most start in the fallopian tubes
- Gynecologic symptoms rare -mimics other diseases
- CA125 and TVUS not useful and should not be used to screen for HGSC
- However CA125 useful for symptomatic women
- Don't hesitate to use it -vague abdominal and constitutional symptoms
 - Serial test more useful than one off test





Key points

- Irregular Bleeding in women over 45 must be investigated by endometrial biopsy
- HGSC of endometrial cancer behave like HGSC ovary
- Minimal symptoms and signs can arise in a background of atrophic endometrium
- **Deaths from OC and endometrial cancer**
3rd most common cause of death in Canadian women

