Hereditary Cancer Syndromes in Women with Gynecologic Cancer

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Disclosures

- None

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Virginia Mason Gyn & Gyn Onc

- **Minimally Invasive Fellowship Trained Gynecologists**
  - **Laparoscopic and Robotic procedures**
    - **Endometriosis**
    - **Chronic Pelvic Pain**
- **Office Based Gynecology**
  - **Well care**
  - **Cervical and other dysplasia and precancer**
  - **NAMS based menopause care**
- **Gynecologic Oncology**
  - **Surgical and Medical oncologists for the continuum of gyn cancer care**

Our aim is to provide

- Timely consultations
  - For oncology care, pts can typically be seen within 3 days
  - For gynecology care, visit with in 2-4 weeks*
- Excellent evidence-based and patient-centered care
  - Fellowship trained minimally invasive surgeons who offer appropriate care
- Communicate our findings and plans
  - We have entered your data into our system to streamline records
  - Open to feedback for improvement
  - Create relationships
- Refer back with a plan of care/follow up

Overview

- Review of ovarian and endometrial cancer
- Hereditary Breast and Ovarian Cancer Syndrome
  - Who to test
  - How to screen
  - Risk reducing surgery
- Lynch Syndrome
  - Who to test
  - How to screen
  - Risk reducing surgery
- Advances in cancer treatment in women with genetic mutations

Ovarian and Primary Peritoneal Cancer

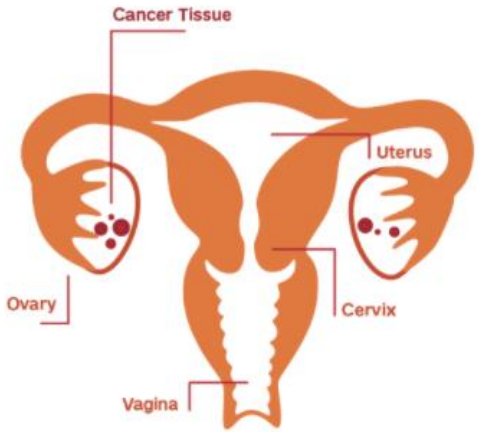
- Approximately 1 in 78 women will develop in lifetime
- In 2021:
  - About 21,410 women will receive a new diagnosis of ovarian cancer.
  - About 13,770 women will die from ovarian cancer.
- 5 year overall survival for patients with advanced disease: 30%
- Approximately 80% of women with advanced disease will have a recurrence at 5 years
  - Recurrent disease is not curable

Ovarian and Primary Peritoneal Cancer

- Cancers that start in the ovary, fallopian tube, or lining of the abdominal cavity
- Often present at advanced stage as this is when patients develop symptoms
  - Bloating
  - Urinary urgency/frequency
  - Early satiety
  - Pelvic pain

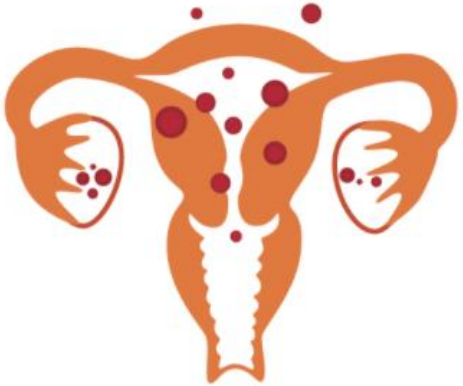
Ovarian Cancer

Stage 1



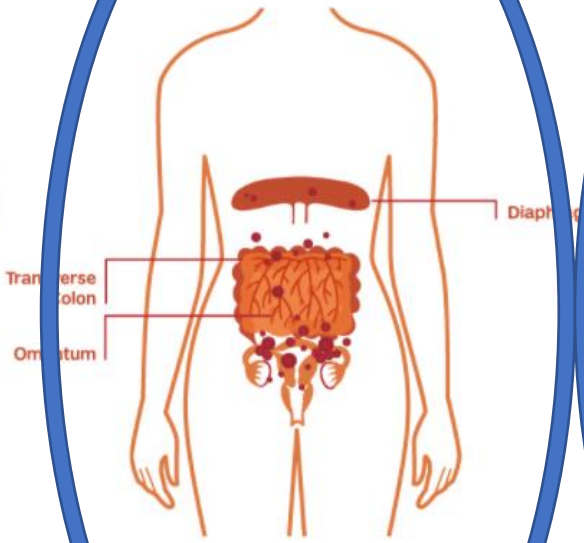
Cancer is found in one or both ovaries.

Stage 2



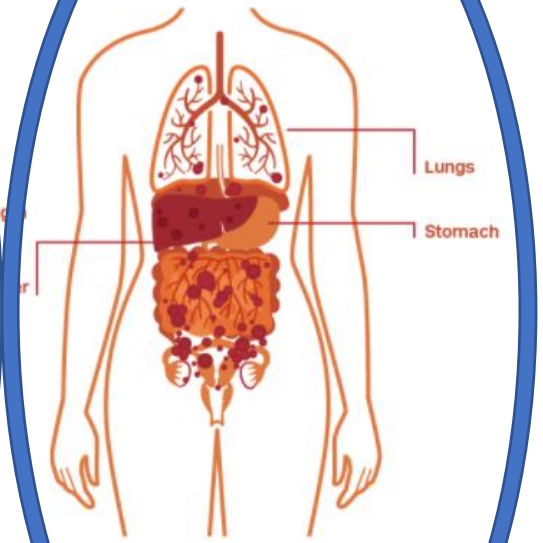
Cancerous cells have spread from the ovaries to other parts of the pelvis, such as the fallopian tubes or uterus.

Stage 3



Cancerous cells have spread outside the pelvis to the nearby lymph nodes, diaphragm, intestines, or liver.

Stage 4



The cancer has spread beyond the abdomen, such as to the lungs or spleen.

Ovarian and Primary Peritoneal Cancer

- Different types
  - Epithelial ovarian cancer
    - Serous
    - Endometrioid
    - Clear cell
    - Carcinosarcoma
  - Stromal tumors
  - Germ cell tumors

Ovarian and Primary Peritoneal Cancer

- Primary treatment consists of a combination of chemotherapy and surgery
  - Order of treatment depends on location of disease – is it amenable to surgical resection?
  - May or may not be followed by maintenance therapies depending on stage and patient factors

Ovarian and Primary Peritoneal Cancer

- Approximately 20-25% of women who develop ovarian cancer have a genetic mutation predisposing them to breast and ovarian cancer
- Less than 1% of the general population have these mutations

High Penetrance Breast and Ovarian Cancer Genes

ATM	BARD1	BRCA 1 and 2*
BRIP 1*	CDH1	CHEK2
MLH1, PMS2, MSH2, MSH6, EPCAM*	NBN	NF1
PALB2	PTEN	RAD51C and D*
STK11	TP53	

Hereditary Breast and Ovarian Cancer Syndrome

- Testing for individuals for high penetrance breast and ovarian cancer genes that puts them at increased risk for disease
- Who do we test?

Who to test?

- Individuals with any blood relative with a known pathogenic cancer susceptibility gene

Who to test, continued

- Patients with a personal history of cancer
  - Epithelial ovarian cancer
    - This excludes less common types of ovarian cancers such as germ cell or granulosa cell tumors
    - Can be difficult to elucidate this history
  - Breast cancer diagnosed at age </= 45 years old
  - Breast cancer diagnosed at age 46-50 with:
    - Unknown or limited family history
    - A second breast cancer diagnosed at any age
    - One or more close relatives with breast, pancreatic, ovarian, or prostate cancer at any age
  - Triple negative breast cancer diagnosed at age </= 60 years old

Who to test, continued

- Patients with a personal history of breast cancer diagnosed at any age, AND
  - Ashkenazi Jewish ancestry
  - Close family relative with
    - Breast cancer diagnosed < 50 years old
    - Ovarian cancer
    - Pancreatic Cancer
    - Metastatic or high risk prostate cancer
  - >/= 3 close family members with a diagnosis of breast cancer

Who to test, continued

- Patients with a personal history of pancreatic cancer

Who to test, continued

- Patients with a personal history of prostate cancer with
  - Metastatic disease
  - Cribiform histology
  - High risk group (defined in NCCN prostate cancer guidelines)
  - Ashkenazi Jewish ancestry
  - Close relative with breast cancer </= 50 years old, ovarian cancer, pancreatic cancer, metastatic or high risk prostate cancer
  - >/= 2 close relatives with any breast or prostate cancer

Who to test, continued

- Anyone with any family history of the above

Who to Test

- Patients who have been previously tested for any of the above criteria, but were only tested for single gene testing and are interested in pursuing multi-gene testing

Multi-Gene Panel Testing

- Advantages
  - Casting a wider net
  - The more we discover about genes that may impact breast and ovarian cancer risk, the more gene panels expand to include testing for these mutations
- Disadvantages
  - Increased risk for finding variants of unknown significance (VUS)
- Important to have patient meet with a genetic counselor to review risks and benefits

A Note About Genetic Counselors

- An invaluable resource
- A limited resource
- Important for patient care

Management of Patients with Hereditary Breast and Ovarian Cancer Syndrome

- Can we screen for ovarian cancer?
  - Good screening tests need to be:
    - Inexpensive
    - Easy to administer
    - Minimal discomfort
    - Reliable (consistent)
    - Valid (distinguish between diseased and non-diseased individuals)
      - High sensitivity (high probability of detecting disease)
      - High specificity (high probability that those who do not have the disease will screen negative)

Ovarian cancer “screening”

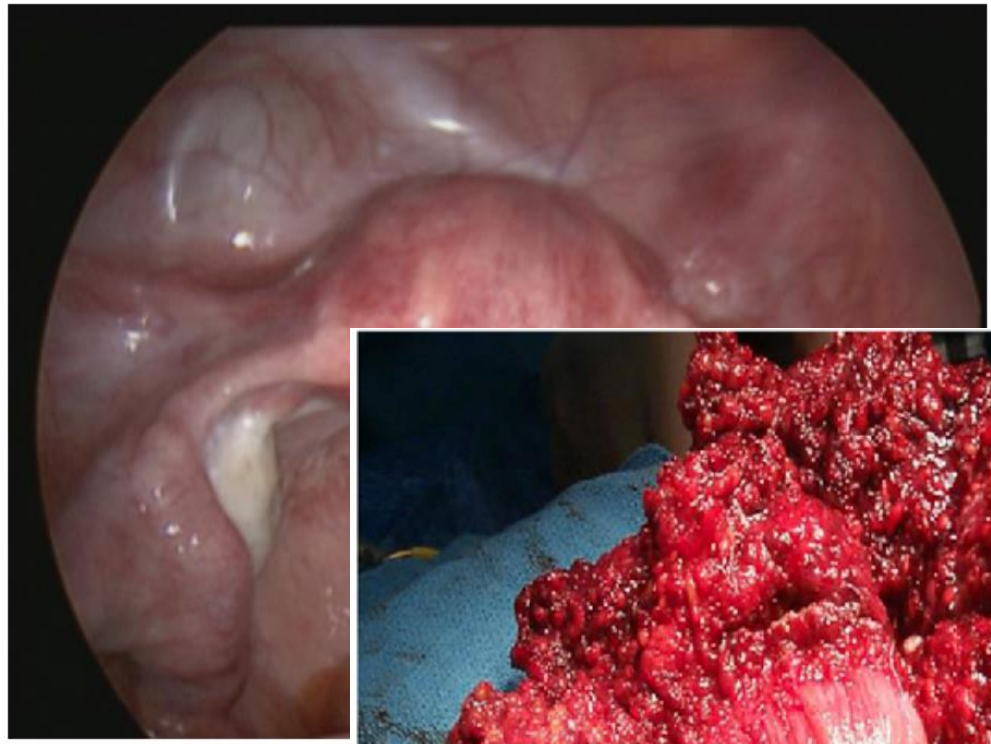
- NCCN guidelines recommend transvaginal ultrasound and Ca-125 levels in women with BRCA mutations specifically, starting at age 30-35
- Can be performed in 6 month to one year intervals
- Described as “uncertain benefit”
- Transvaginal ultrasounds and Ca-125 levels have a high false positive rate
  - Often leads to anxiety and surgery for benign ovarian cysts
- Important to have a discussion regarding risks and benefits with the patient

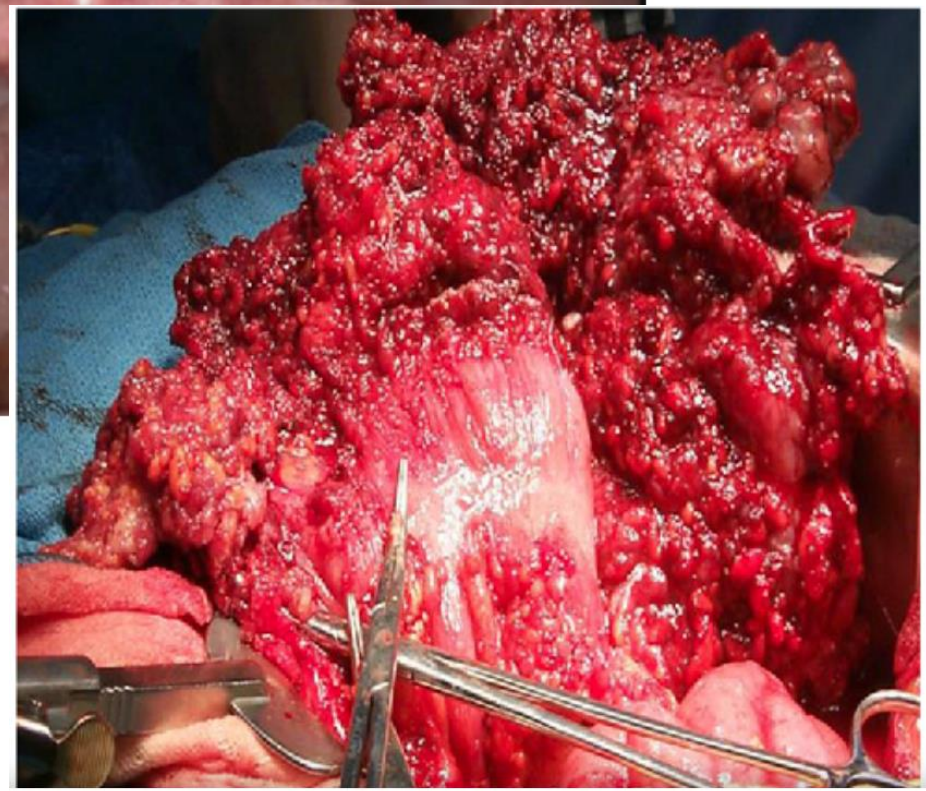
Risk reducing surgery for ovarian cancer prevention

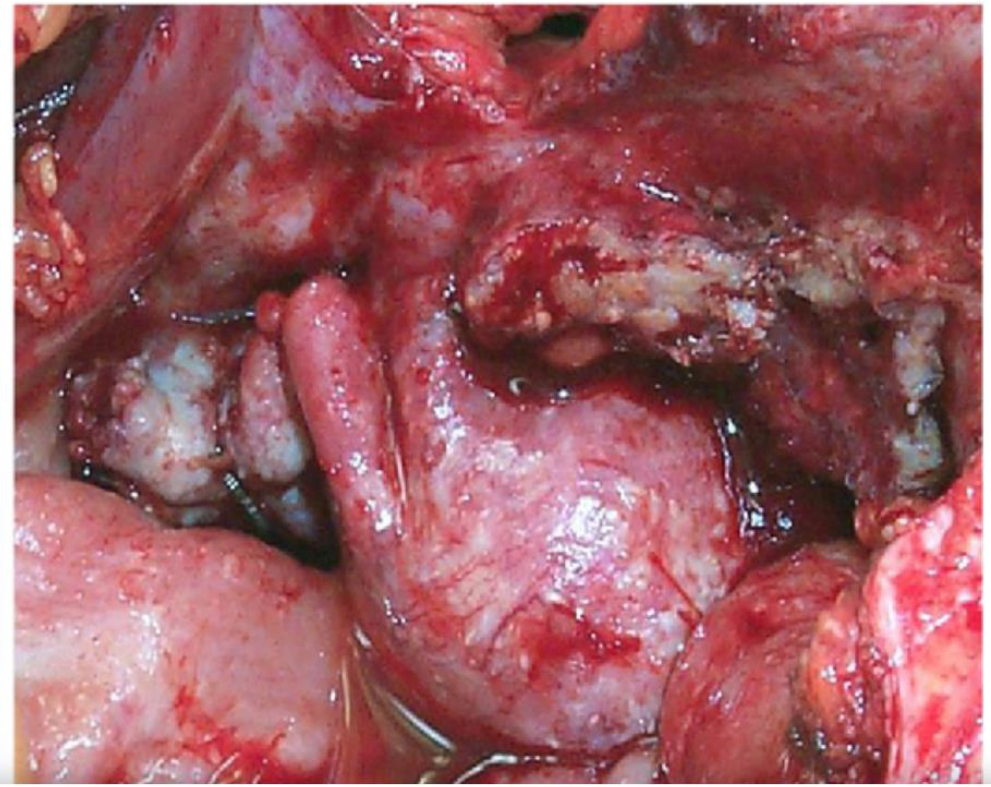
- BRCA-1 patients
  - Risk reducing bilateral salpingo-oophorectomy (removal of tubes and ovaries) after completion of childbearing and after the age of 35-40 years old
- BRCA-2 patients
  - Risk reducing bilateral salpingo-oophorectomy after completion of childbearing and after the age of 40-45 years old
- Risk reducing bilateral salpingo-oophorectomy is also recommended for the following genetic mutations:
  - BRIP-1 at age 45-50 years old
  - RAD51C and D at age 45-50 years old

How to perform a risk reducing surgery

- Laparoscopic
- Pelvic washings
- Should remove 2cm of gonadal vessel proximal to the ovary
- Should do a complete abdominopelvic survey
- If any concern for cancer implants, these should be biopsied and sent for frozen section
  - If cancer, discontinue procedure
- Serial sectioning by pathology







Endometrial Cancer

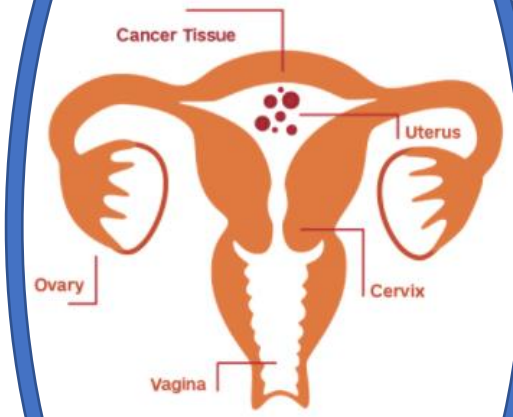
- Most common gynecologic cancer diagnosed in the United States
- In 2021:
  - About 66,570 new cases of cancer of the body of the uterus (uterine body or corpus) will be diagnosed.
  - About 12,940 women will die from cancers of the uterine body.

Endometrial Cancer

- Most common presenting symptom
  - Postmenopausal vaginal bleeding
  - Abnormal uterine bleeding
- Risk factors
  - Obesity
  - Metabolic syndrome
  - Unopposed estrogen replacement therapy
  - All thought to be related to an excess estrogenic state

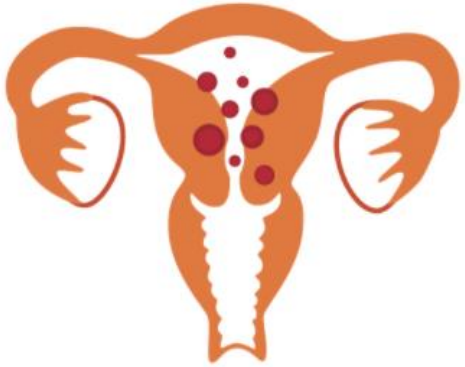
Uterine Cancer

Stage 1



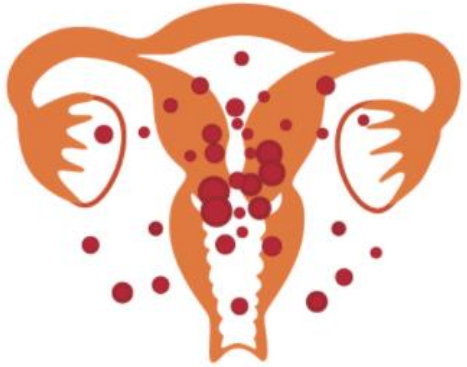
Cancerous cells are found only in the uterus.

Stage 2



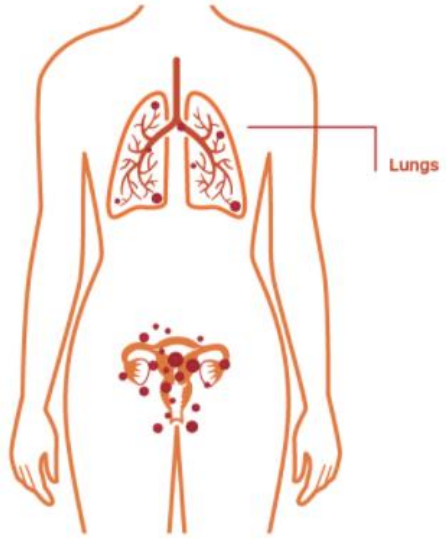
The cancer has spread to the cervix (opening of the uterus).

Stage 3



The cancer has spread outside the uterus to the nearby lymph nodes, ovaries, fallopian tubes, or vagina. It has not spread to the bladder, rectum, outside the pelvis.

Stage 4



The cancer has spread to the bladder, rectum, or outside the pelvis, such as the lungs or abdomen.

Endometrial Cancer

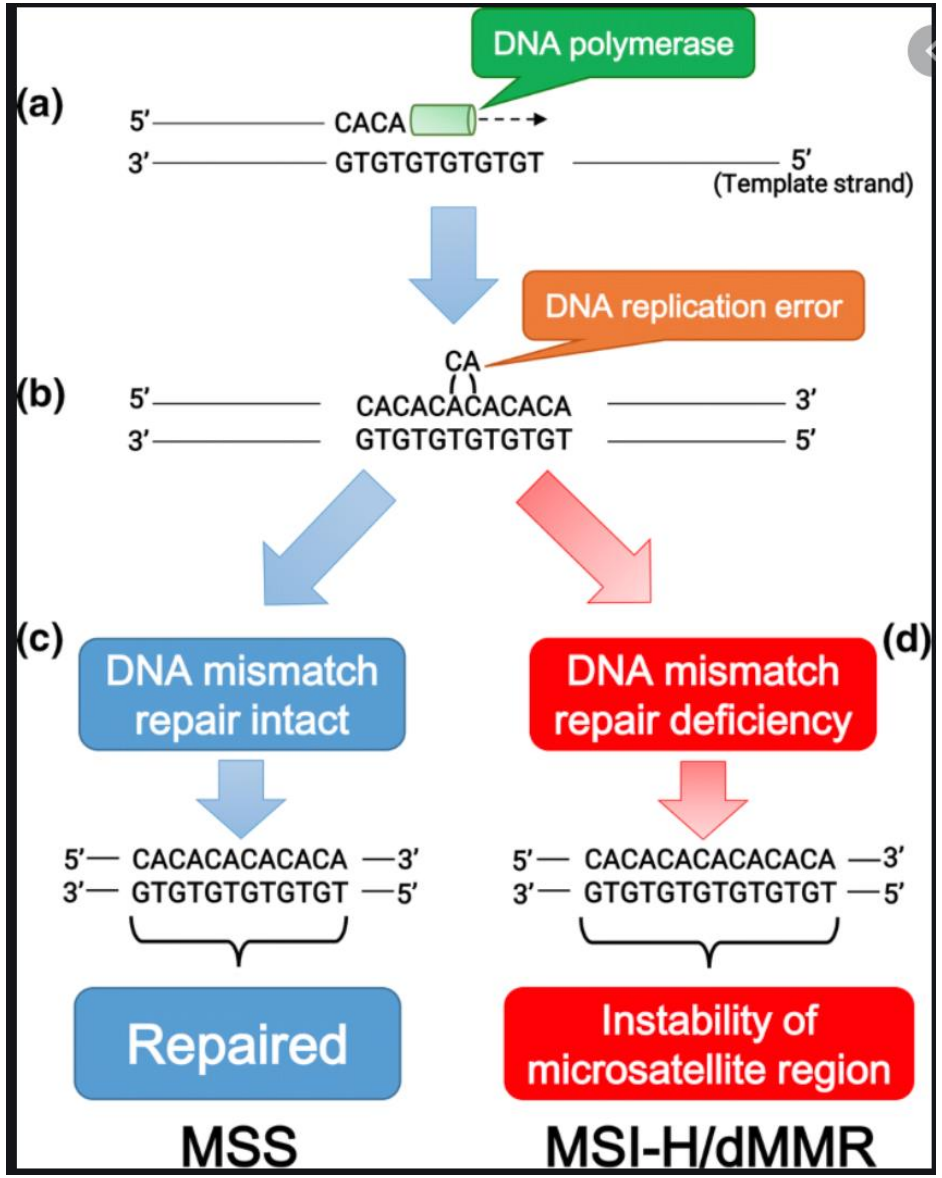
- Vast majority are diagnosed at an early stage
- 5 year overall survival with early stage endometrial cancer: 95%
  - 5 year overall survival with advanced stage disease: 17%
- Treatment includes surgical staging, +/ - radiation therapy and chemotherapy

Genetic Mutations Related to Endometrial Cancer

- Lynch Syndrome
  - Mutations in the mismatch repair protein pathway
  - MLH1
  - PMS2
  - MSH2
  - MSH6
- 10% of endometrial cancers are hereditary

Lynch Syndrome

Mutations in the mismatch repair pathway



Endometrial and Ovarian Cancer Risks

MLH1

- Endometrial cancer cumulative risk: 34-54%, average age 49 years old
- Ovarian cancer cumulative risk: 4—20%, average age 46 years old

MSH2

- Endometrial cancer cumulative risk: 21-57%, average age 47-48 years old
- Ovarian cancer cumulative risk: 8-38%, average age 43 years old

MSH6

- Endometrial cancer cumulative risk: 16-49%, average age 53-55 years old
- Ovarian cancer cumulative risk: < 1-16%, average age 46 years old

PMS2

- Endometrial cancer cumulative risk: 12-36%, average age 49-50 years old
- Ovarian cancer cumulative risk: 3%, average age 51-59 years old

Who to Test

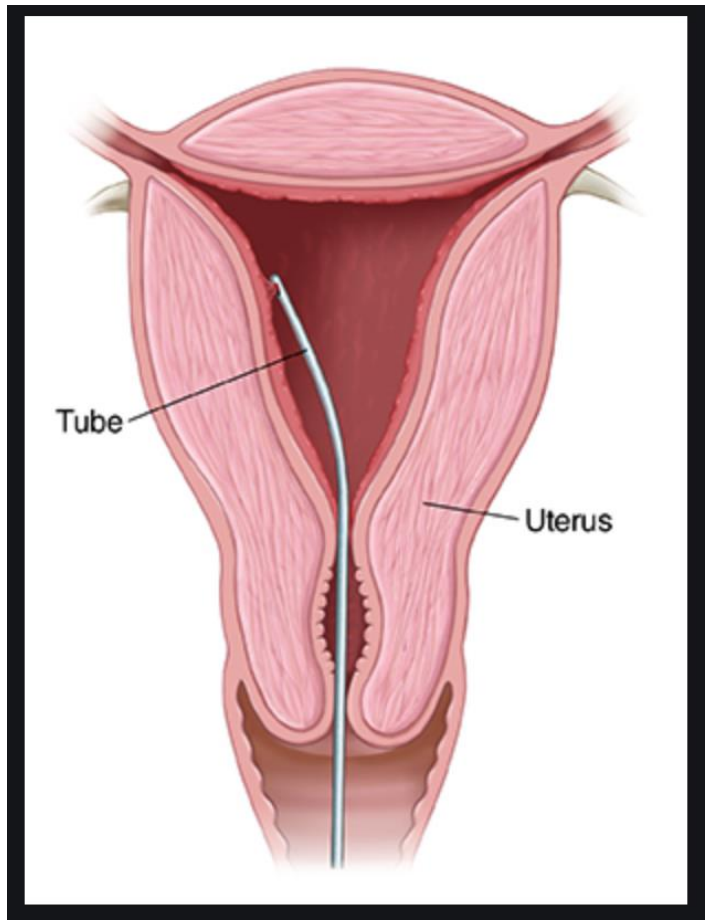
- Personal history of colorectal cancer or endometrial cancer AND
  - Diagnosed < 50 years old
  - Diagnosis of another Lynch syndrome related cancer (colorectal, endometrial, ovarian, gastric, pancreatic, urothelial, brain, biliary tract)
  - One first degree or second degree relative with Lynch syndrome related cancer diagnosed < 50 years old
  - >/= 2 first degree or second degree relatives with Lynch syndrome related cancers, regardless of age

Who to test, continued

- Family history of
  - >/= 1 first degree relative with colorectal or endometrial cancer diagnosed < 50 years old
  - >/= 1 first degree relative with colorectal or endometrial cancer and another lynch syndrome related cancer
  - >/= two first degree or second degree relatives with lynch syndrome related cancers, including at least one diagnosed < 50 years old
  - >/= three first or second degree relatives with lynch syndrome related cancers

Endometrial cancer screening

- No proven benefit
- However, endometrial biopsy is highly specific and sensitive
- Recommend endometrial biopsies every 1-2 years starting at age 30-35 years old


Tube
Uterus

Risk reducing surgery

- Hysterectomy is recommended, usually prior to age 50
- However, timing should be based on
  - Completion of childbearing
  - Specific genetic mutation, as risks vary by pathogenic variant
  - Family history
  - Comorbidities

Is there an indication for oophorectomy with Lynch Syndrome?

- Short answer – YES
- But risk depends on the mutation

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Why do we care?

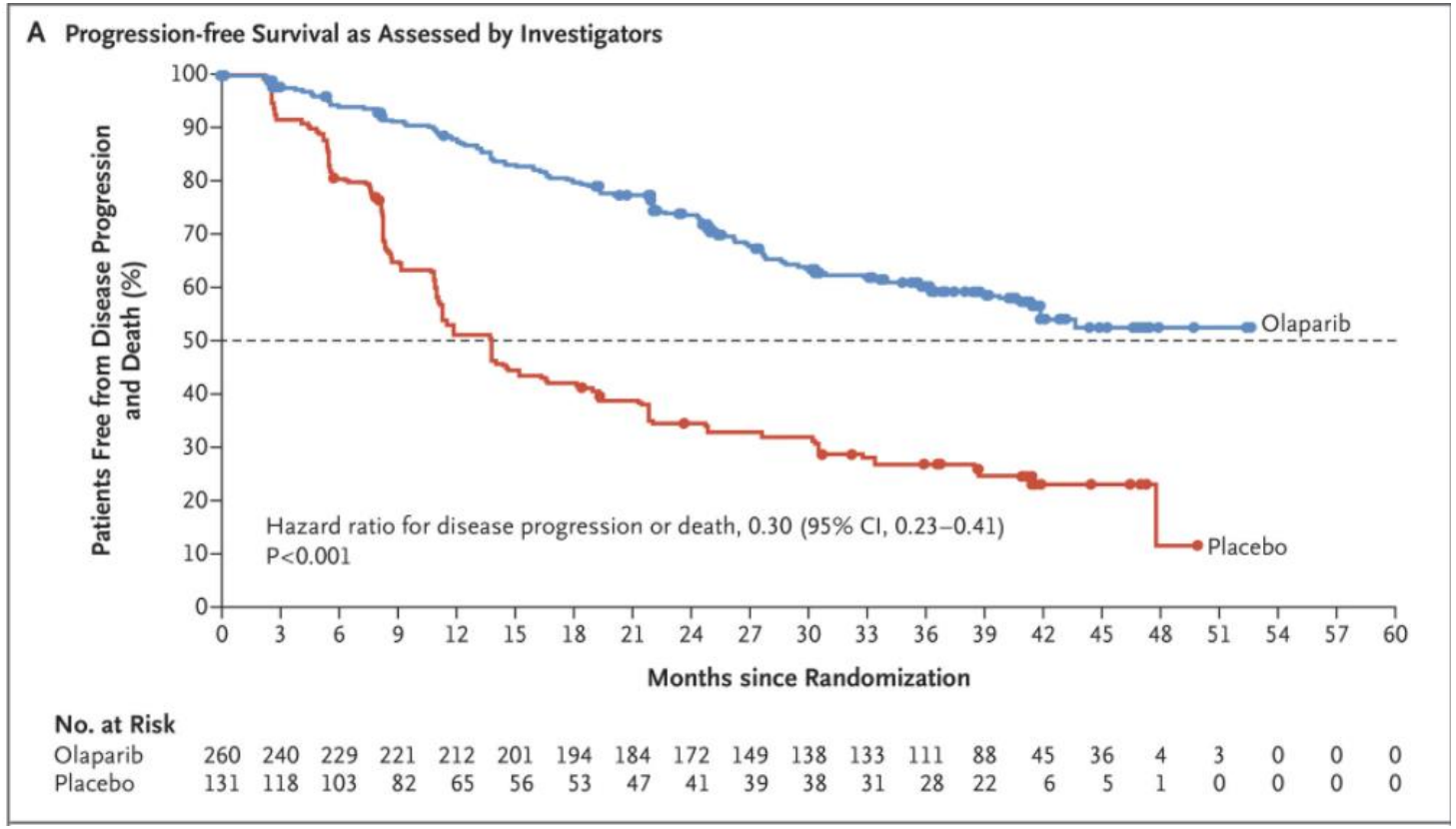
- In women with hereditary cancer syndromes, we have an opportunity to prevent gynecologic cancers with appropriate surgical interventions
- Genetic mutations can inform cancer directed therapies

Parp Inhibition in Ovarian Cancers

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

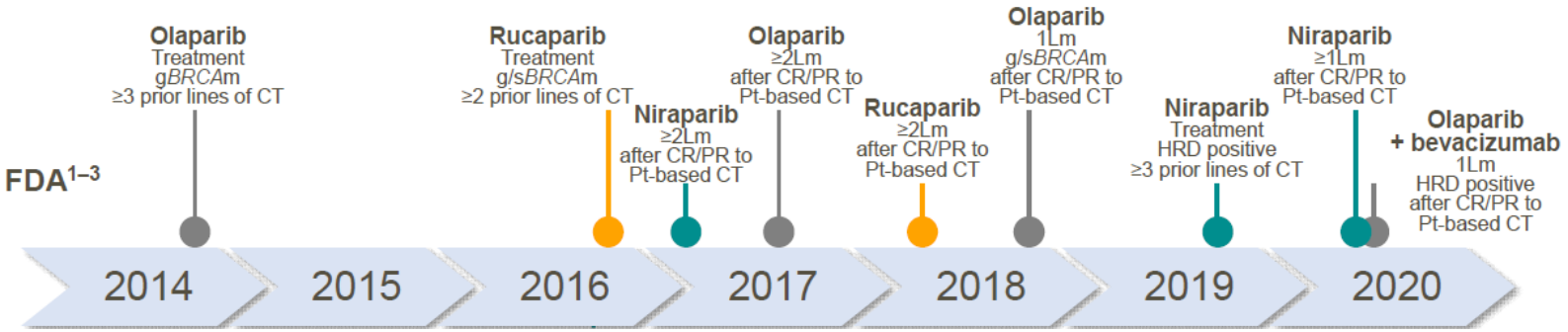
Kathleen Moore, M.D., Nicoletta Colombo, M.D., Giovanni Scambia, M.D., Byoung-Gie Kim, M.D., Ph.D., Ana Oaknin, M.D., Ph.D., Michael Friedlander, M.D., Alla Lisyanskaya, M.D., Anne Floquet, M.D., Alexandra Leary, M.D., Gabe S. Sonke, M.D., Ph.D., Charlie Gourley, M.D., Ph.D., Susana Banerjee, M.D., Ph.D., et al.



Parp Inhibition in Ovarian Cancers

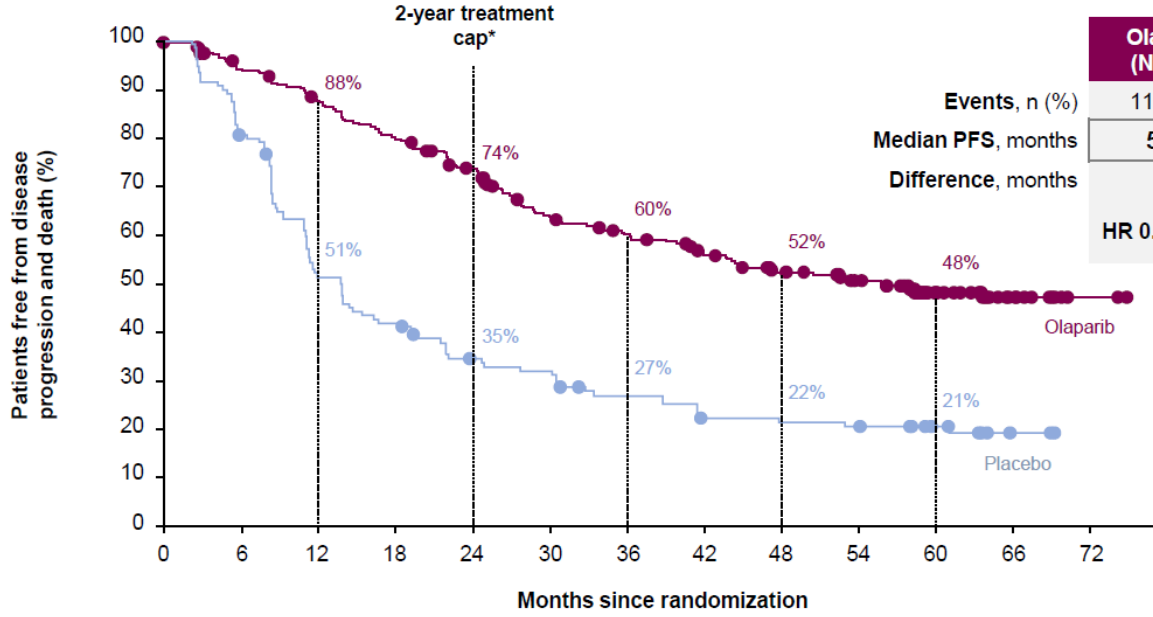
Approvals of PARPi for Advanced OC

- PARPi have changed the treatment paradigm for the management of advanced OC



Parp Inhibition in Ovarian Cancers

PFS benefit of maintenance olaparib was sustained beyond the end of treatment



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
HR 0.33 (95% CI 0.25–0.43)		

No. at risk

Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

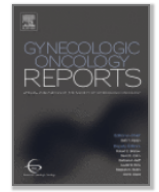
*13 patients, all in the olaparib arm, continued study treatment beyond 2 years; †n=130 (safety analysis set).
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.

Society of Gynecologic Oncology

Immunotherapy in recurrent endometrial cancer

ELSEVIER

Gynecologic Oncology Reports
Volume 33, August 2020, 100581



Long-term durable responses after pembrolizumab immunotherapy for recurrent, resistant endometrial cancer

John K. Chan [a], David S. Lakomy [b], Yassmina McDonald [a], Daniel S Kapp [c]

Summary

- Women are at risk for hereditary breast and ovarian cancer syndrome and Lynch syndrome
- These syndromes increase a patient's risk for gynecologic cancers including ovarian and endometrial cancer
- When diagnosed, there is an opportunity for cancer prevention with risk reducing surgery
  - A thorough family history can prevent a cancer diagnosis
  - Consider risk reducing gynecologic surgery in women with Lynch syndrome, BRCA1/2, BRIP1, RAD51C and D mutations
- Emerging therapies targeting germline and somatic mutations are demonstrating promising results in women's cancer