Hereditary Cancer Syndromes and Gynecologic Malignancies

Allison M. Barrie, MD

Gynecologic Oncology

Saturday, September 9th, 2023

Virginia Mason Franciscan Health™

Disclosures

- None

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 patients with genetic mutations

Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

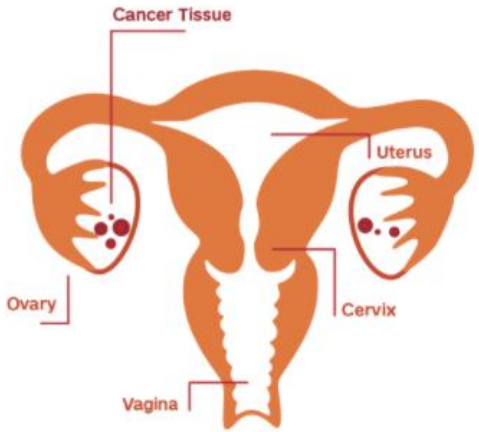
- Approximately 1 in 78 patients will develop in lifetime
- In 2023:
  - About 19,710 patients will receive a new diagnosis of ovarian cancer.
  - About 13,270 patients will die from ovarian cancer.
- 5 year overall survival for patients with advanced disease: 30%
- Approximately 80% of patients with advanced disease will have a recurrence at 5 years
  - Recurrent disease is not curable

Ovarian, Fallopian Tube, 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

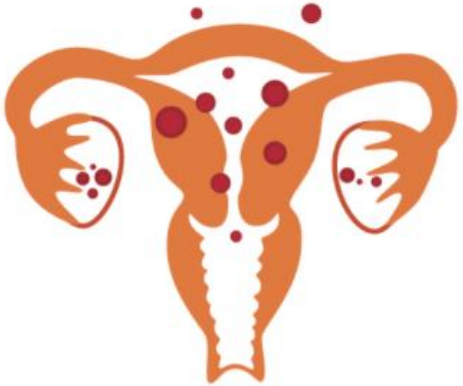
Ovarian Cancer

Stage 1



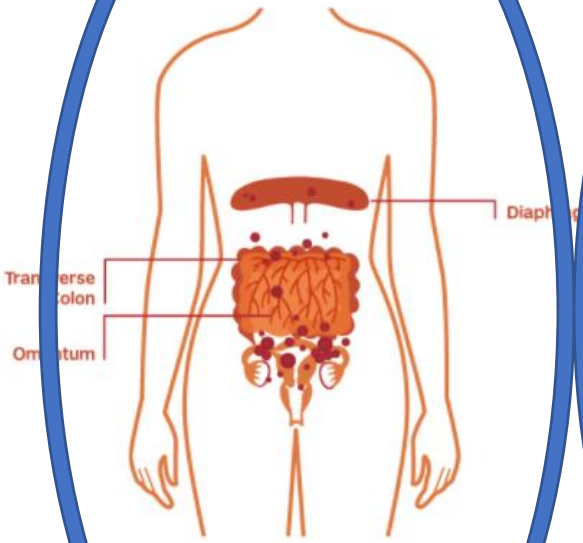
Cancer is found in one or both ovaries.

Stage 2



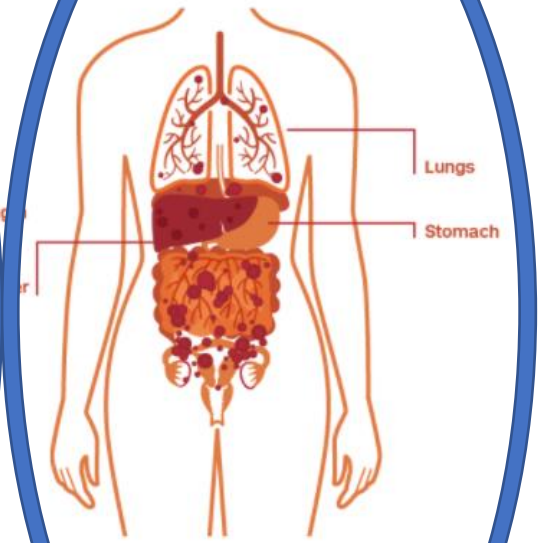
Cancerous cells have spread from the ovaries to other parts of the pelvis, such as the fallopian tubes or uterus.

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, Fallopian Tube, and Primary Peritoneal Cancer

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

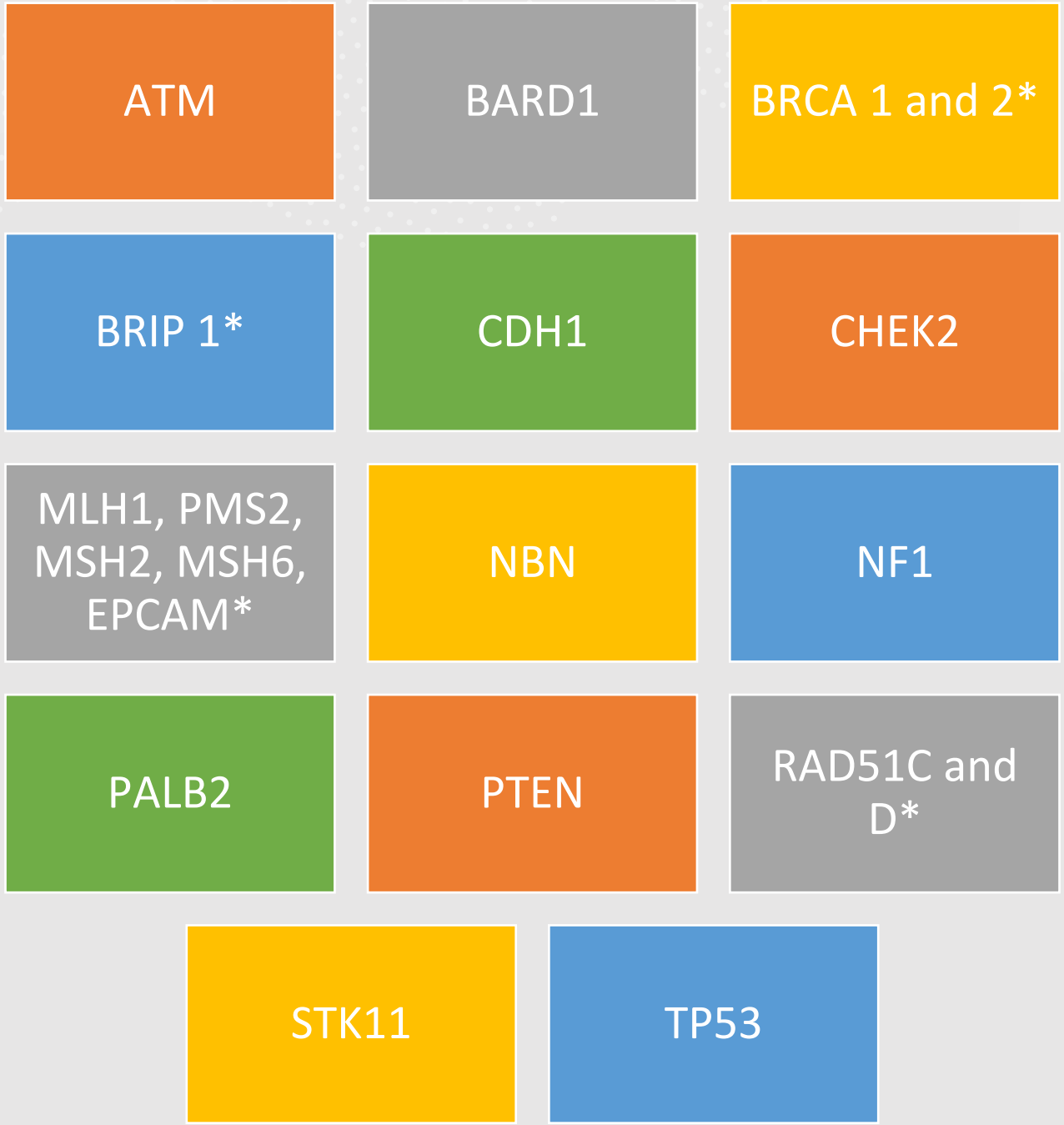
Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

- 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, Fallopian Tube, and Primary Peritoneal Cancer

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

High Penetrance Breast and Ovarian Cancer Genes



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?

Family and Medical History Screening

- First degree relatives (parents, siblings, children)
- Second degree relatives (grandparents, aunts, uncles, grandchildren, nieces, nephews, half siblings)
- Clarification on maternal vs paternal sides
- Ashkenazi ancestry
- For each cancer case, establish age at diagnosis and primary disease site

Who to test?

- Cancer diagnosed at unusually young age or < 50 for breast, ovary, or colon
- Several different types of cancers in one patient
- Multiple primary tumors, especially breast or colon, in the same patient
- Several close blood relatives with the same type of cancer
- Unusual presentation of a specific type of cancer (breast cancer in a male)
- Specific benign conditions associated with cancer syndromes (skin growths, skeletal abnormalities)
- Triple negative breast cancer
- Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer
- Colorectal cancer or endometrial cancer with mismatch repair deficiency

Who to test?

National Comprehensive Cancer Network®

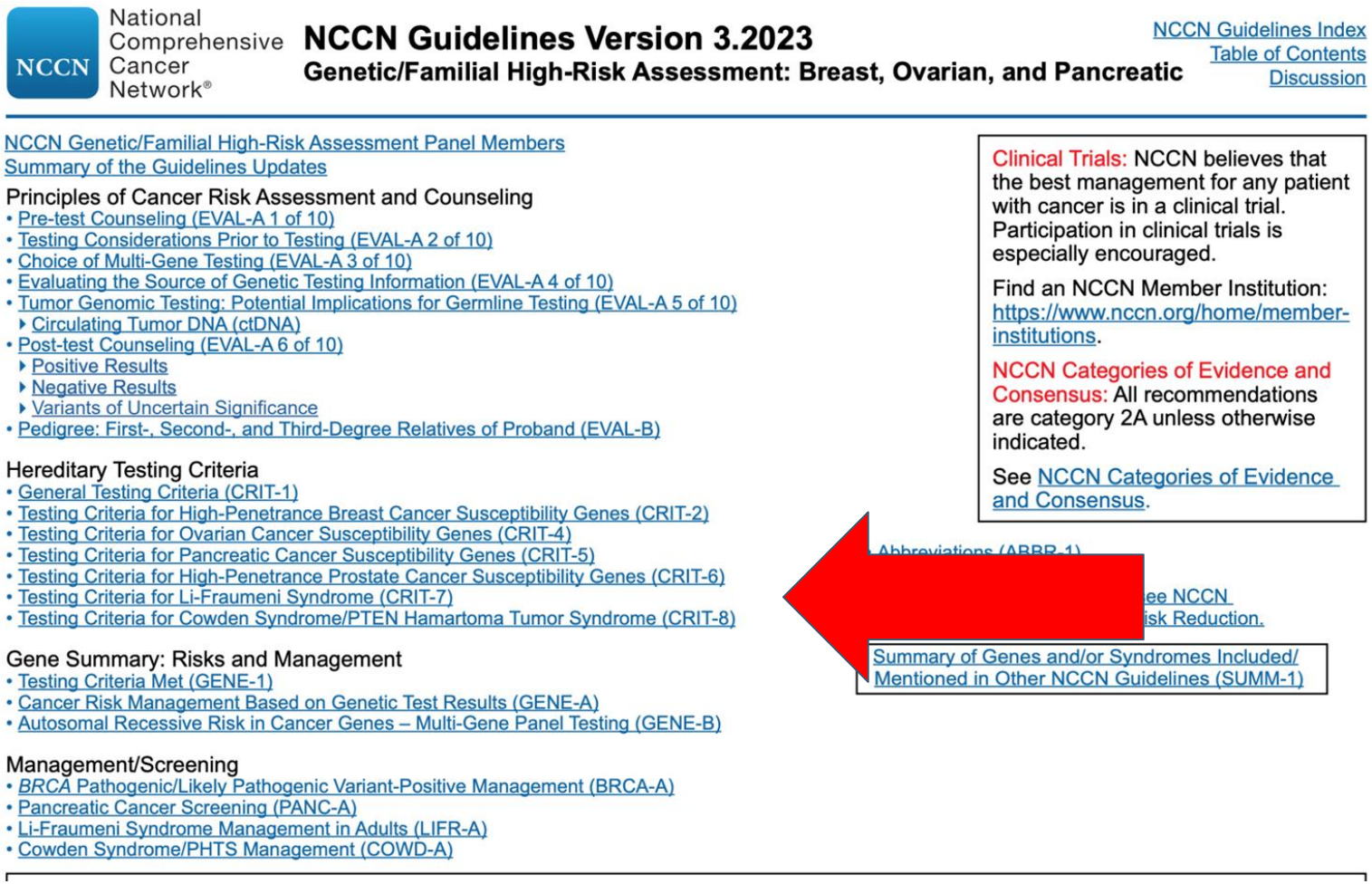
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Version 3.2023 — February 13, 2023

NCCN.org

Who to test?



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Genetic/Familial High-Risk Assessment Panel Members
Summary of the Guidelines Updates

Principles of Cancer Risk Assessment and Counseling
- Pre-test Counseling (EVAL-A 1 of 10)
- Testing Considerations Prior to Testing (EVAL-A 2 of 10)
- Choice of Multi-Gene Testing (EVAL-A 3 of 10)
- Evaluating the Source of Genetic Testing Information (EVAL-A 4 of 10)
- Tumor Genomic Testing: Potential Implications for Germline Testing (EVAL-A 5 of 10)
  - Circulating Tumor DNA (ctDNA)
- Post-test Counseling (EVAL-A 6 of 10)
  - Positive Results
  - Negative Results
  - Variants of Uncertain Significance
- Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B)

Hereditary Testing Criteria
- General Testing Criteria (CRIT-1)
- Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes (CRIT-2)
- Testing Criteria for Ovarian Cancer Susceptibility Genes (CRIT-4)
- Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-5)
- Testing Criteria for High-Penetrance Prostate Cancer Susceptibility Genes (CRIT-6)
- Testing Criteria for Li-Fraumeni Syndrome (CRIT-7)
- Testing Criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (CRIT-8)

Gene Summary: Risks and Management
- Testing Criteria Met (GENE-1)
- Cancer Risk Management Based on Genetic Test Results (GENE-A)
- Autosomal Recessive Risk in Cancer Genes – Multi-Gene Panel Testing (GENE-B)

Management/Screening
- *BRCA* Pathogenic/Likely Pathogenic Variant-Positive Management (BRCA-A)
- Pancreatic Cancer Screening (PANC-A)
- Li-Fraumeni Syndrome Management in Adults (LIFR-A)
- Cowden Syndrome/PHTS Management (COWD-A)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

Abbreviations (ABBR-1)

ee NCCN
isk Reduction.

Summary of Genes and/or Syndromes Included/ Mentioned in Other NCCN Guidelines (SUMM-1)

Who to test?

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Hereditary Cancer Testing Criteria

NCCN Guidelines Index
Table of Contents
Discussion

GENERAL TESTING CRITERIA[a]

Testing is clinically indicated in the following scenarios:

- Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene
- Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing
- A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline
- To aid in systemic therapy and surgical decision-making[b]
- Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (see CRIT-7) or Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) testing criteria (see CRIT-8) or Lynch syndrome See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- For personal or family history of
  - Breast cancer — See Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes (CRIT-2)
  - Ovarian cancer — See Testing Criteria for High-Penetrance Ovarian Cancer Susceptibility Genes (CRIT-4)
  - Pancreatic cancer — See Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-5)
  - Prostate cancer — See Testing Criteria for Prostate Cancer Susceptibility Genes (CRIT-6)
  - Colorectal cancer — See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

Testing *may be* considered in the following scenario (with appropriate pre-test education and access to post-test management):

- An individual of Ashkenazi Jewish ancestry[c] without additional risk factors
- Personal history of serous endometrial cancer[d]

For a list of NCCN Guidelines that include content focused on inherited cancer conditions, including criteria for testing and/or cancer risk management based on a genetic test result, see Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines (SUMM-1).

Who to test?

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,e,f,g]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - ≤50 y
  - Any age:
    - ◊ Treatment indications
      - – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[h,i] (See NCCN Guidelines for Breast Cancer)
      - – To aid in adjuvant treatment decisions with olaparib for high-risk,[j] HER2-negative breast cancer[h]
    - ◊ Pathology/histology
      - – Triple-negative breast cancer
      - – Multiple primary breast cancers (synchronous or metachronous)[k]
      - – Lobular breast cancer with personal or family history of diffuse gastric cancer See NCCN Guidelines for Gastric Cancer
    - ◊ Male breast cancer
    - ◊ Ancestry: Ashkenazi Jewish ancestry
  - Any age (continued):
    - ◊ Family history[l]
      - – ≥1 close blood relative[m] with ANY:
        - ▪ breast cancer at age ≤50
        - ▪ male breast cancer
        - ▪ ovarian cancer
        - ▪ pancreatic cancer
        - ▪ prostate cancer with metastatic,[n] or high- or very-high-risk group (Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
      - – ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
      - – ≥2 close blood relatives[m] with either breast or prostate cancer (any grade)
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[o]
    - ◊ If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[p]

Criteria met → See GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Who to test, continued

- Family history of 1st or 2nd degree relative with epithelial ovarian cancer
- Family history of 1st degree relative with exocrine pancreatic cancer

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

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”

- Can consider transvaginal ultrasound and Ca-125 levels in women with BRCA mutations specifically, starting at age 30-35 until risk reducing surgery
- 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 unnecessary surgical intervention
- Important to have a discussion regarding risks and benefits with the patient

Risk reducing surgery for ovarian cancer prevention

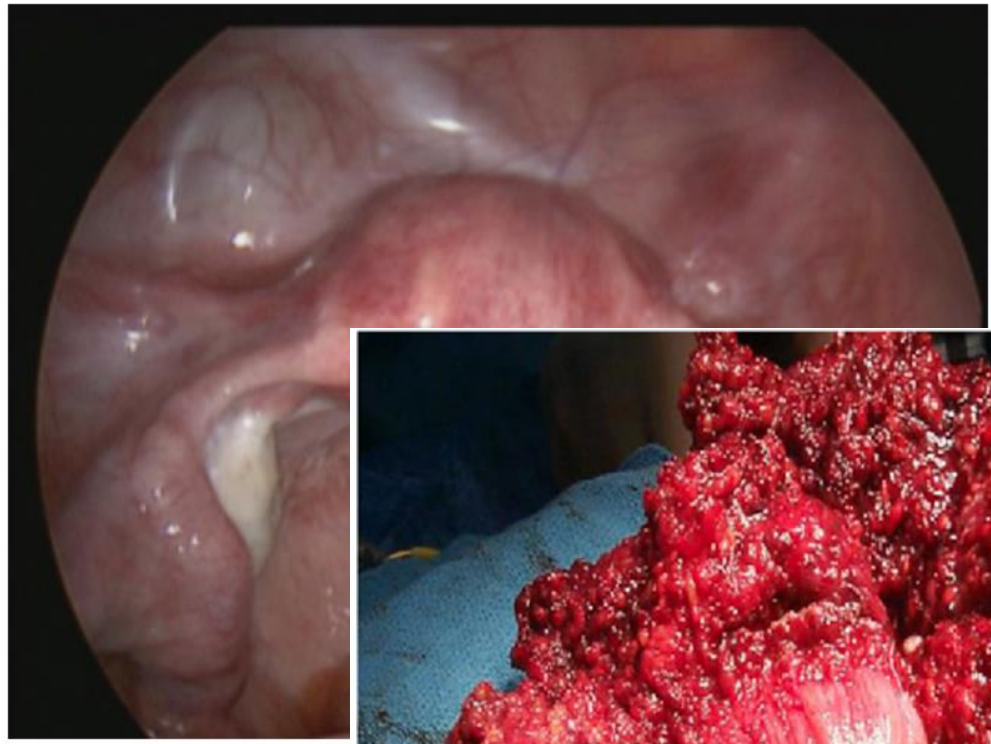
- BRCA-1 patients
  - Risk reducing bilateral salpingo-oophorectomy (removal of tubes and ovaries) after completion of childbearing and after the age of 35-40 years old
- BRCA-2 patients
  - Risk reducing bilateral salpingo-oophorectomy after completion of childbearing and after the age of 40-45 years 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

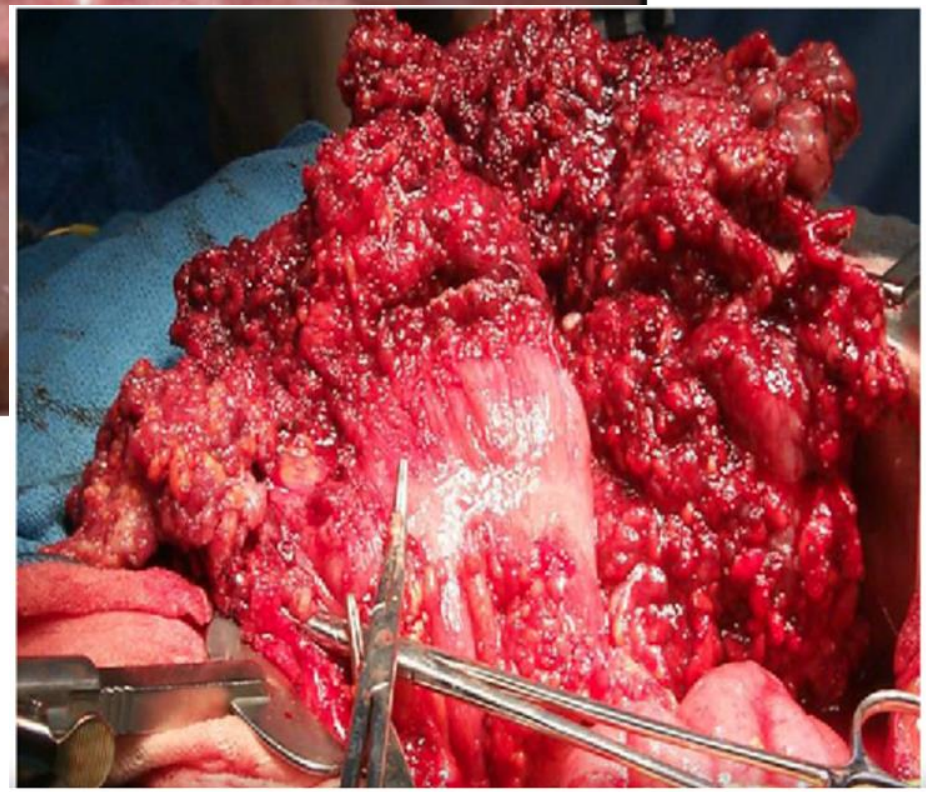
What about hysterectomy ?

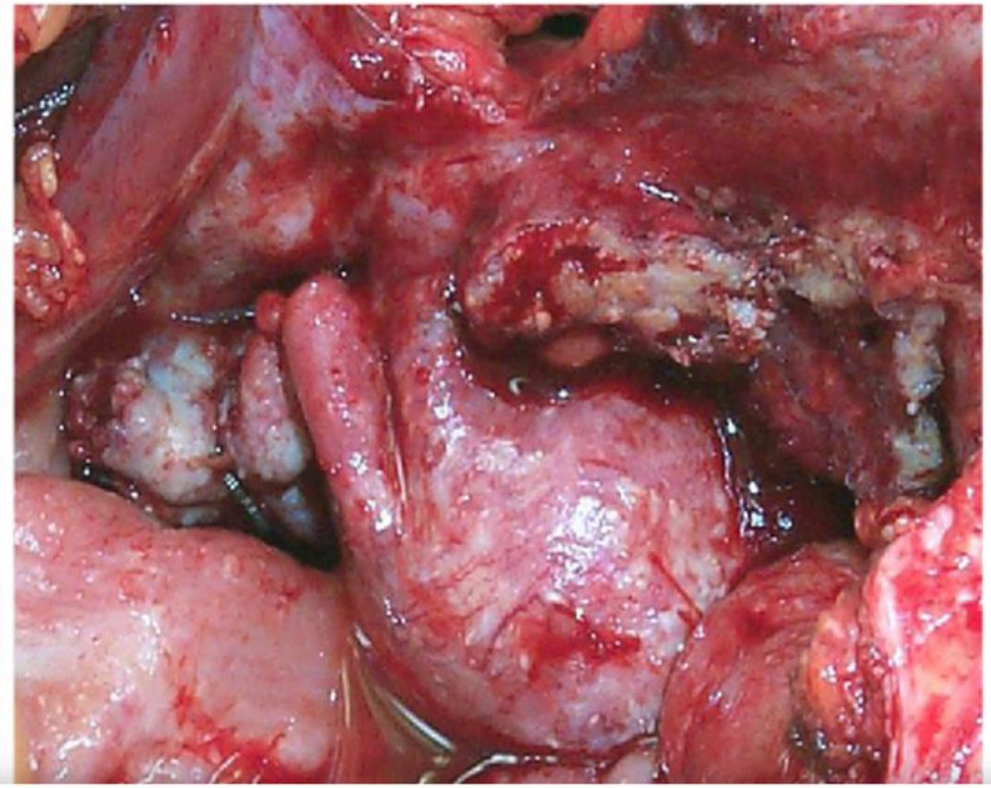
- BRCA-1 patients
  - Increased risk for uterine serous carcinoma
- Simplify hormone therapy strategy
- Can be considered when there are other medical indications for removal of uterus and cervix
- Reduce endometrial cancer risk for patients taking Tamoxifen

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 (SEE-Fim protocol)







Endometrial Cancer

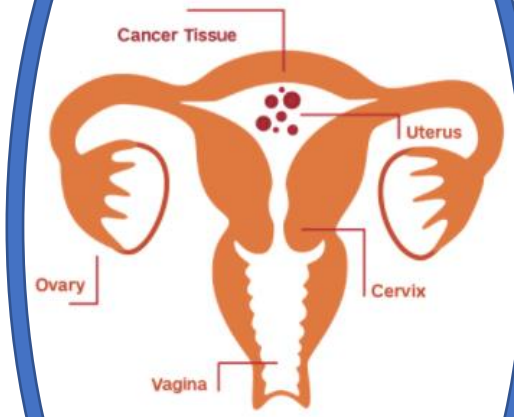
- Most common gynecologic cancer diagnosed in the United States
- In 2023:
  - About 66,200 new cases of cancer of the body of the uterus (uterine body or corpus) will be diagnosed.
  - About 13,030 women will die from cancers of the uterine body.

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

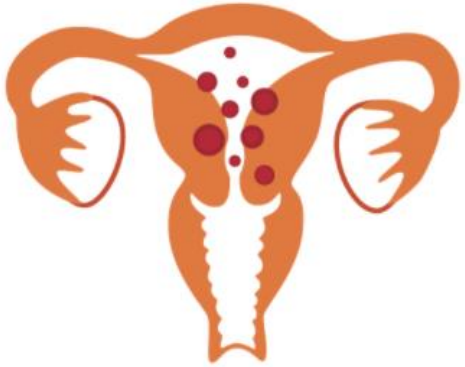
Uterine Cancer

Stage 1



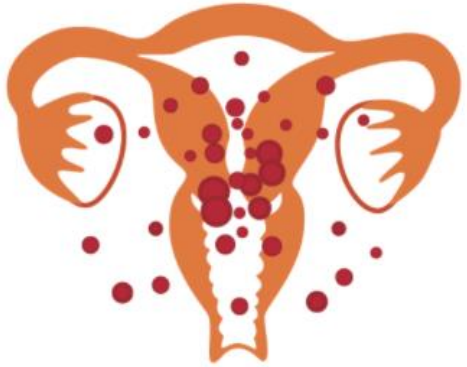
Cancerous cells are found only in the uterus.

Stage 2



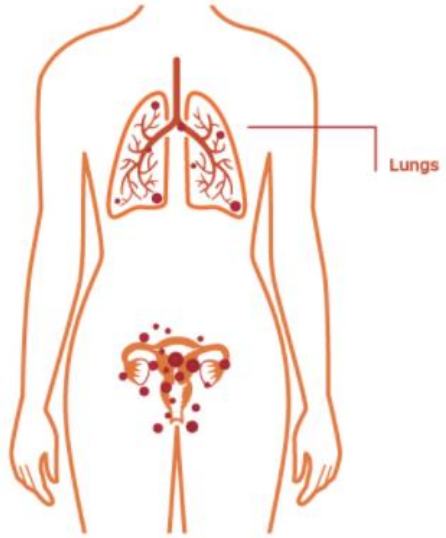
The cancer has spread to the cervix (opening of the uterus).

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

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

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Colorectal

Version 2.2022 — December 7, 2022

NCCN.org

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

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?

- Yes
- Risk depends on the mutation

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

Why do we care?

- In patients 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 Cancer

Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial

Paul DiSilvestro, MD[1]; Susana Banerjee, MD, PhD[2]; Nicoletta Colombo, MD, PhD[3]; Giovanni Scambia, MD[4]; Byoung-Gie Kim, MD, PhD[5]; Ana Oaknin, MD, PhD[6]; Michael Friedlander, MD[7]; Alla Lisyanskaya, MD[8]; Anne Floquet, MD[9,10]; Alexandra Leary, MD[10,11]; Gabe S. Sonke, MD, PhD[12]; Charlie Gourley, MD, PhD[13]; Amit Oza, MD[14]; Antonio González-Martín, MD, PhD[15,16]; Carol Aghajanian, MD[17]; William Bradley, MD[18]; Cara Mathews, MD[1]; Joyce Liu, MD[19]; John McNamara, MSc[20]; Elizabeth S. Lowe, MD[21]; Mei-Lin Ah-See, MB BChir, MD[22]; and Kathleen N. Moore, MD[23]; on behalf of the SOLO1 Investigators

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.

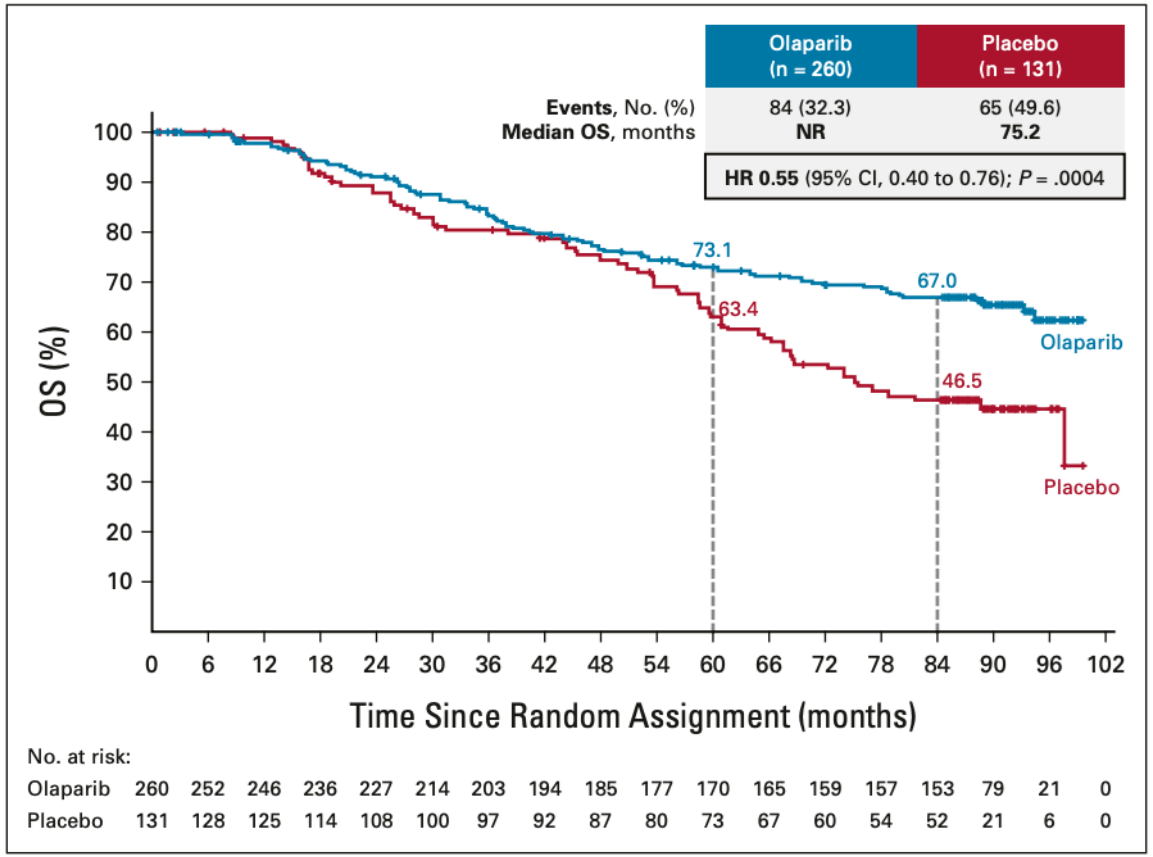
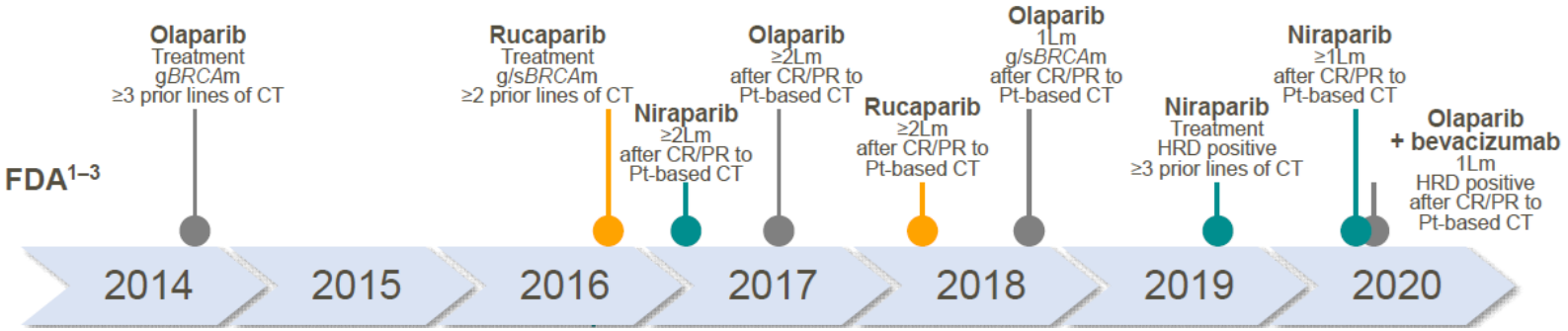


FIG 2. Kaplan-Meier estimates of OS. HR, hazard ratio; NR, not reached; OS, overall survival.

PARP Inhibition in Ovarian Cancers

Approvals of PARPi for Advanced OC

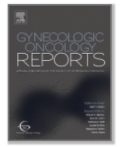
- PARPi have changed the treatment paradigm for the management of advanced OC



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]

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., et al.

Summary

- Patients 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 gynecologic cancers