Hereditary Cancer Risk Assessment for Gynecological Cancers

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Objectives

• Review Cancer Genetics Basics

• Review Hereditary Cancer Syndromes

• Why Multi Genetic testing?

• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
All Cancer is Genetic...

First mutation → Second mutation → Third mutation → Fourth mutation → Malignant cells tumor growth
The Genesis of Cancer

- Environmental factors (90%)
  - Carcinogens
    - Tobacco, Radiation, Asbestos, Sunlight
  - Diet
    - Stomach cancer (Japan)
    - Esophageal cancer (China)
    - Colorectal cancer (USA)
- Immunodeficiency
- Hormonal factors
  - Prostate cancer
  - Breast cancer
  - Endometrial cancer
- Infectious Agents
  - Epstein-Barr virus
  - H. Pylori
  - Human papilloma virus
  - Hepatitis B virus
  - Schistosomiasis
- Genetic predisposition
What Causes Cancer

- **70-80% sporadic**
- **10-20%**
- **5-10% hereditary**

**Sporadic Cancer**
- Happens in one person or possibly two distantly related family members at older ages

**Familial Cancer**
- A clustering of cancer in a family that may be due to genes and/or other shared factors, such as environment and lifestyle

**Hereditary Cancer**
- A clustering of cancer in a family due to inherited gene changes (mutations), which can be passed from parent to child
Cancer begins with a genetic change in a cell, and is thus always related to genetics, BUT, not often inherited.

Most changes are random events (sporadic) that occur in SOMATIC cells throughout someone’s lifetime, but SOME are in the germline and SOME are inherited.

People born with a tumor suppressor gene mutation are already “one step closer” to developing a tumor, but may never develop a tumor.

Genetic profiles of tumors are different than germline genetic testing because you do not know if the genetic changes in the tumor are acquired or inherited.
<table>
<thead>
<tr>
<th>Germline Mutations</th>
<th>Somatic Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>In every cell</td>
<td>In tumor cells</td>
</tr>
<tr>
<td>Stable and do not change</td>
<td>Not stable, may appear and disappear over time</td>
</tr>
<tr>
<td>Impact cancer risks</td>
<td>Impact cancer risks</td>
</tr>
<tr>
<td>Impact treatment regimen</td>
<td>Impact treatment regimen</td>
</tr>
<tr>
<td>Inherited</td>
<td>Not inherited</td>
</tr>
</tbody>
</table>
Inheritance

• 2 copies of each autosomal gene (one copy from each parent)
• Autosomal dominant: only needs one altered copy to have a predisposition to cancer
• Autosomal recessive: both copies of the gene need to be altered to have a predisposition to cancer
• X-linked: gene present on the X chromosome, may present differently in males vs. females

Most cancer syndromes are inherited in an autosomal dominant manner, but some are recessive

Benefits of Genetic Testing

**SCREEN**

Option to modify frequency and initial age of mammogram/breast MRI, colonoscopy, prostate cancer screening, or other screening as appropriate

**PREVENT**

Consideration of prophylactic mastectomy, colectomy, or other risk-reducing measures, as appropriate

**TREAT**

Option to tailor chemotherapy strategies and/or determine eligibility for clinical trials

**KNOW**

Identify at-risk family members
Objectives

• Review Cancer Genetics Basics

• Review Hereditary Cancer Syndromes
  • BRCA ½
  • Lynch Syndrome
  • Hereditary Diffuse Gastric Cancer
  • Li-Fraumeni Syndrome
  • Other Cancer Risk Genes

• Why Multi Genetic testing?

• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessmen
**BRCA1/2: The Most Common Hereditary Ovarian Cancer Genes**

<table>
<thead>
<tr>
<th>FREQUENCY</th>
<th>CANCER RISKS</th>
<th>IMPACTS THE FAMILY</th>
<th>ACTIONABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs in 1/400 individuals, or 1/40 individuals of Ashkenazi Jewish descent</td>
<td>Breast&lt;br&gt;Ovarian&lt;br&gt;Prostate&lt;br&gt;Pancreatic&lt;br&gt;Male Breast</td>
<td>Children, siblings, parents have a 50% chance of having the same mutation as the patient</td>
<td>Medical management guidelines exist for the multiple cancer risks</td>
</tr>
</tbody>
</table>

**ALSO KEY:**
Presence of a *BRCA1/2* is also a major factor for PARP inhibitor eligibility
# Hereditary Cancer Syndromes: BRCA1/2

<table>
<thead>
<tr>
<th>CANCER TYPE</th>
<th>GENERAL POPULATION RISK</th>
<th>BRCA1 MUTATION RISK</th>
<th>BRCA2 MUTATION RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12%</td>
<td>46-72%</td>
<td>38-69%</td>
</tr>
<tr>
<td>Second breast</td>
<td>25%</td>
<td>40-47%</td>
<td>26-47%</td>
</tr>
<tr>
<td>Ovarian/fallopian tube/primary peritoneal</td>
<td>1-2%</td>
<td>34-44%</td>
<td>12-20%</td>
</tr>
<tr>
<td>Male breast</td>
<td>0.1%</td>
<td>Increased</td>
<td>7%</td>
</tr>
<tr>
<td>Prostate</td>
<td>16%</td>
<td>Increased</td>
<td>20-30%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0.9%</td>
<td>3-4%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.6%</td>
<td>Unestablished</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Sources:**


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### Hereditary Cancer Syndromes: Lynch Syndrome

- **AKA:** Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
- **Mutation in** *MLH1, MSH2, PMS2, MSH6,* or *EPCAM* gene
- **Recessive disease risk** = CMMRD/ BMMRD (Constitutional/Biallelic Mismatch Repair Deficiency)
- **Tumor screening** may include microsatellite instability (MSI) and immunohistochemistry (IHC) analysis
- **Amsterdam II** or Revised Bethesda are commonly used, but broader testing criteria also exist (see NCCN, 2016)

**Table:**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>Risk w/ MLH1 or MSH2 mutation</th>
<th>Risk w/ MSH6 mutation</th>
<th>Risk w/ PMS2 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>52-82%</td>
<td>10-22% (may be higher in males)</td>
<td>15-20%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.7%</td>
<td>25-60%</td>
<td>16-26%</td>
<td>15%</td>
</tr>
<tr>
<td>Gastric</td>
<td>&lt;1%</td>
<td>6-13%</td>
<td>&lt;3%</td>
<td>6% combined risk for these cancers (excluding sebaceous neoplasms and pancreas)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.6%</td>
<td>4-24%</td>
<td>1-11%</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1-4%</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Small bowel, Brain/CNS, hepatobiliary tract, sebaceous neoplasms, pancreatic</td>
<td>&lt;1% each</td>
<td>1-9% each</td>
<td>unknown</td>
<td></td>
</tr>
</tbody>
</table>

**Sources:**


**Created by ACOG District II in 2017 / Updated August 2017**
Hereditary Cancer Syndromes: Hereditary Diffuse Gastric Cancer (HDGC)

- Clinical diagnostic criteria from International Gastric Cancer Linkage Consortium: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991043/
- CDH1 gene mutations in 25-50% of those who meet HDGC criteria
  - High risk screening still needed for those who meet criteria but do not have an identifiable mutation
- Increased cancer risks:

<table>
<thead>
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<th>Cancer Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIFFUSE Gastric Cancer</td>
<td>67-83%</td>
</tr>
<tr>
<td>LOBULAR Breast Cancer</td>
<td>39-52%</td>
</tr>
<tr>
<td>SIGNET RING Colorectal Cancer?*</td>
<td>unclear</td>
</tr>
</tbody>
</table>

*NOTE: Although there are case reports of colorectal and appendiceal signet ring cell carcinomas (SRCCs) in CDH1 mutation carriers, there is currently no evidence to suggest that the risk of colorectal cancer in CDH1 mutation carriers is significantly elevated and there are insufficient data to inform recommendations on colorectal cancer screening. Some families with specific findings may warrant increased screening. See most recent IGCLC guidelines for further information.


PAY ATTENTION TO PATHOLOGY. IT CAN GIVE YOU CLUES!!
Hereditary Cancer Syndromes: Li-Fraumeni Syndrome

- **TP53** gene
- Rare: 1/5,000 - 1/20,000
- 7-20% new mutation rate (there may be no family history)
- Diagnostic Criteria: Classic LFS Criteria and Revised Chompret criteria (see NCCN guidelines)
- Large spectrum of cancer risks, early age of onset, multiple primary cancers
- Overall 21-49% risk of cancer by age 30, and a lifetime risk of up to 68-100% (higher in women)

Core tumors account for 70% of LFS cancers

- Soft tissue sarcoma
- Breast cancer (all women with breast cancer ≤ age 30 should be offered testing for LFS)
- Brain tumors
- Adrenocortical carcinoma

ALSO: Choroid plexus tumor, leukemia, lung cancer, gastrointestinal cancers, genitourinary cancers, neuroblastoma/other childhood cancers, skin, thyroid

### Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>107 (49-203)</td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>61 (33-102)</td>
</tr>
<tr>
<td>Brain</td>
<td>35 (19-60)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7.3 (2-19)</td>
</tr>
<tr>
<td>Breast</td>
<td>6.4 (4.3-9.3)</td>
</tr>
<tr>
<td>Colon</td>
<td>2.8 (1-6)</td>
</tr>
<tr>
<td>Liver</td>
<td>1.8 (2.1-64)</td>
</tr>
</tbody>
</table>

NCCN GUIDELINES FOR DETECTION, PREVENTION, & RISK REDUCTION: Genetic/Familial High-Risk Assessment: Breast and Ovarian v2.2017

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Objectives

• Review Cancer Genetics Basics

• Review Hereditary Cancer Syndromes

• Why Multi Genetic testing?

• Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
“Other” Hereditary Cancer Predisposition Genes

- In addition to those described, there are many other known genes that cause increased cancer risks, and more genes are being discovered.
- Our understanding of the spectrum of cancer types and the magnitude of cancer risk for each gene continues to evolve and change as we learn more.
- Some genes have unique features such as other non-cancerous clinical findings, recessive disease risk, and common genetic variants.

***REFER TO THE APPENDIX FOR COMPREHENSIVE SUMMARY TABLES THAT DESCRIBE THE CLINICAL FEATURES OF THESE GENES***

Breast Cancer Risk
- BRCA1/2
- TP53
- CDH1
- PTEN
- ATM
- CHEK2
- PALB2
- RAD51C/RAD51D
- STK11

Gyn Cancer Risk
- BRCA1/2
- Lynch Syndrome
- PTEN
- PALB2
- STK11
- FH
- BRIP1
- RB1
- SMARCA4

Other Common Risk Genes You May Encounter
- APC
- MUTYH
- Many more...

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Causes of Breast Cancer

- Sporadic, 70-80%
- Familial, 15-20%
- Hereditary, 5-10%
- BRCA1 and BRCA2 (up to 50%)
- Additional Genes in Breast Cancer Panels (12-30%)
- Unknown
Increased Likelihood of Identifying an Important Mutation
Study of 337 patients with breast cancer who underwent panel testing

Pathogenic Mutations in Panel Group

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>48%</td>
</tr>
<tr>
<td>NON-BRCA1/2</td>
<td>52%</td>
</tr>
</tbody>
</table>

Distribution of Non-BRCA1/2 Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>15%</td>
</tr>
<tr>
<td>CHEK2</td>
<td>15%</td>
</tr>
<tr>
<td>MRE11A</td>
<td>8%</td>
</tr>
<tr>
<td>MSH2</td>
<td>8%</td>
</tr>
<tr>
<td>NBN</td>
<td>8%</td>
</tr>
<tr>
<td>PALB2</td>
<td>23%</td>
</tr>
<tr>
<td>MUTYH</td>
<td>15%</td>
</tr>
</tbody>
</table>

REFERENCE
Hereditary ovarian cancer has many genetic etiologies.

- **BRCA1/2**: 20-40%
- **Lynch syndrome**: 10%
- **Peutz-Jeghers (STK11)**: 20%
- **SMARCA4**: Not well quantified
- **DICER1**: Not well quantified
- **BRIP1, RAD51C, RAD51D**: Not well quantified

Why does it make sense to consider panel testing?
Hereditary cancer has many genetic etiologies.

<table>
<thead>
<tr>
<th>Well Known Causes of Hereditary Uterine Cancer</th>
<th>Lifetime Uterine Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td>Up to 60%</td>
</tr>
<tr>
<td>Cowden syndrome (PTEN)</td>
<td>10%</td>
</tr>
<tr>
<td>Li-Fraumeni (TP53)</td>
<td>Not well quantified</td>
</tr>
</tbody>
</table>
# Gynecological Cancer Genes Beyond BRCA1/2 and Lynch

<table>
<thead>
<tr>
<th>Gynecological Cancer Genes</th>
<th>BRIP1 RAD51C RAD51D</th>
<th>PTEN</th>
<th>PALB2</th>
<th>STK11</th>
<th>TP53</th>
<th>DICER1 SMARCA4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gynecological cancer risks and management</strong></td>
<td>Consider risk-reducing oophorectomy between ages 45-50</td>
<td>Consider risk-reducing hysterectomy for endometrial cancer lifetime risk ~28%</td>
<td>Possible increased risk for ovarian cancer</td>
<td>Increased risks for non-epithelial ovarian, cervical, and uterine cancers</td>
<td>~90% overall lifetime cancer risk, including gynecological cancers</td>
<td>Associated with rare ovarian cancer types</td>
</tr>
<tr>
<td><strong>Other cancer risks and management</strong></td>
<td>Possible increased risk for breast cancer</td>
<td>Also associated with increased risks for breast, thyroid, renal, and colorectal neoplasms (benign and malignant)</td>
<td>Significantly increased risk for breast cancer</td>
<td>Also associated with increased risk for breast, lung, pancreatic, GI, and testicular cancers</td>
<td>Also associated with increased risk for breast &amp; brain cancers, leukemia, sarcoma, others</td>
<td>DICER1: Ovarian sex cord-stromal tumors SMARCA4: Small cell carcinoma of the ovary, hypercalcemic type</td>
</tr>
</tbody>
</table>
Objectives

- Review Cancer Genetics Basics
- Review Hereditary Cancer Syndromes
- Why Multi Genetic testing?
- Discuss the Obstetrician-Gynecologist and Family History-Based Risk Assessment
Guidelines Agree: Ob/Gyns Should Gather a Family History

“A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment should be performed by the obstetrician-gynecologists…and should be updated regularly.” (ACOG, 2015)

ACOG: Ethical Issues in Genetic Testing (CO #410, 2008)
Family History as a Risk Assessment Tool (CO #478, 2011)
Hereditary Cancer Syndromes and Risk Assessment (CO #634, 2015)

ACMG/NSGC: Referral Indications for Cancer Predisposition Assessment (2014)

ASCO: Genetic and Genomic Testing for Cancer Susceptibility (policy, 2015)
Hereditary Colorectal Cancer Syndromes (clinical practice guideline, 2014)

USPSTF: BRCA-related Cancer: Risk Assessment, Genetic Counseling & Genetic Testing (2013)

Genetic Testing for Ovarian Cancer (clinical practice statement, 2014)


NCCN: Genetic/Familial High Risk: Colorectal (guideline, 2016)
Genetic/Familial High Risk Assessment, Breast/Ovarian (v2.2017)

EGAPP: Genetic Testing Strategies (2009)

Please consult individual organizations for any updates to these guidelines after August 2017.

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Cancer Family History as a Screening Tool

 Guidelines support the need for a detailed and updated family history as part of the patient’s OB/GYN medical record. (see ACOG Committee Opinion #478, #634)

• Family history is an essential part of overall health history, and should include:
  • 3 generation family history noting diagnoses and age of onset
  • Male relatives with cancer
  • Paternal family history (equally as important)
  • Genetic testing that has been performed
  • Distinguish primary vs. metastatic cancer
  • Ethnicity of all 4 grandparents
  • Notation of precursor lesions
  • Notation of relevant prophylactic surgeries

• Ob-gyns should have a low threshold for recommending consultation with genetics professionals for unusual histories or outcomes

• Update the history with any new cases of cancer or other hereditary disorders at each visit
Who to Test: Signs of Hereditary Cancer

- **Multiple**
  - 2 OR MORE primary cancers in the same person
  - 3 OR MORE cancers on the same side of the family
  - 10 OR MORE colorectal polyps in a person’s lifetime

- **Young**
  - ANY OF THE FOLLOWING CANCERS DIAGNOSED ≤50Y:
    - Breast, colorectal, uterine

- **Rare**
  - MALE BREAST CANCER, OVARIAN CANCER

- **Ancestry**
  - ASHKENAZI JEWISH AND HISTORY OF BREAST OR PANCREATIC CANCER
Genetic Testing is Recommended by Key Professional Organizations

Society of Gynecologic Oncology

SGO recommends that all women diagnosed with epithelial ovarian, Fallopian tube, and peritoneal cancers should receive genetic counseling and consider genetic testing, even in the absence of a family history of cancer.

*Adapted from SGO Clinical Practice Statement, October 2014*

SGO recommends that women diagnosed with endometrial cancer should be assessed for Lynch syndrome. In addition, women with a family history of endometrial and colon cancer should pursue genetic counseling, regardless of whether they have been diagnosed with cancer.

*Adapted from SGO Clinical Practice Statement, March 2014*
Target Population for Hereditary Breast Cancer Genetic Testing

1. Early-onset breast cancer (diagnosed ≤ 45 years of age)
2. Bilateral or multiple primary breast cancers
3. Male breast cancer at any age
4. Breast and ovarian cancer in the same woman
5. 3 or more cases of breast cancer*
6. 3 or more cases of breast, ovarian, and/or pancreatic cancer*
7. 3 or more cases of breast, uterine, and/or thyroid cancer*
8. Multiple close family members with breast and other cancers*

* On the same side of the family
Pre-Test Genetic Counseling and Informed Consent

**Why**
- Discuss those elements of family history which made them a candidate for genetic testing
- Explain results of this testing may guide cancer screening and prevention recommendations

**What**
- Review the goal of genetic testing in identifying “spelling errors” which lead to increased risk for cancer
- Discuss implications for patient’s medical management
- Explain implications for patient’s family members

**How**
- Blood/saliva sample
- Results available in a few weeks. Set plan to follow-up with results and what will happen next.
Integrating Genetic Testing into Your Practice

Identifying at-risk patients → Pre-Test Genetic Counseling and Informed Consent → Test Ordering and Sample Collection → Results Delivery → Post-Test Genetic Counseling and Medical Management Discussion
Published Assessment Tools: Referral Criteria

• For a detailed list of indication for referral by diverse tumor types, see: ACMG/NSGC Practice Guideline, 2014: Referral Indications for Cancer Predisposition Assessment

• NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian v2.2017, includes: BRCA1/2, Cowden Syndrome, Li-Fraumeni Syndrome, HDGC
  https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection

• NCCN Guidelines Genetic/Familial High Risk Assessment: Colorectal Cancer v1.2016 includes: Lynch syndrome, Polyposis syndromes (APC, MUTYH, Juvenile Polyposis, Serrated Polyposis), Peutz Jeghers syndrome
  https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection

• As previously outlined, some syndromes have established clinical diagnostic criteria: Lynch Syndrome, HDGC, Li-Fraumeni Syndrome, Cowden Syndrome- see Gene Reviews
  https://www.ncbi.nlm.nih.gov/books/NBK1116/
When previous genetic testing was negative or uninformative: new testing options may be available (~20% of detectable mutations are in “new” genes)

For patients with negative family histories: this does NOT rule out the possibility of a hereditary syndrome
  • Could be due to reduced penetrance, early death, prophylactic surgery, small family size, adoption, non-paternity, new mutations in the patient, few female relatives, lack of family communication, random chance
  • Medical and insurance guidelines make exceptions for some of these circumstances if patients are suspicious but don’t meet defined criteria

For patients who were previously assessed low risk: assessments can change over time with new diagnoses, updated family information, examination of medical records
  • People often misreport type of cancer, age of diagnosis
  • Keep updating; ask patient to do some family research

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Guidelines Support Referral

Guidelines support the referral of patients who are assessed to be at increased risk for a hereditary cancer syndrome to a provider with expertise in cancer genetics:

• ACOG Committee Opinion #634, 2015: “If a ...risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education and counseling, which may lead to genetic testing.”

• NCCN Guidelines v1.2017: “…multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.”
While *BRCA1/2* and Lynch syndrome account for the majority of hereditary gynecological cancers, several other genes with associated risks exist.

Multigene panel testing, like OvaNext, is available to detect mutations in known ovarian and uterine cancer genes.

Genetic testing results can have a significant impact on medical management.

SGO and other professional organizations recommend genetic testing for appropriate patients as a standard of care for their medical management.
Per NCCN® guidelines - Mutations must have been detected by an FDA-approved test or other validated test performed by a CLIA-approved laboratory

### Guiding Ovarian Cancer Treatment with Genetic Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutation</th>
<th>Treatment History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>n/a (previously germline BRCA1/2)</td>
<td>Prior 3+ lines of chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also approved for maintenance therapy</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>Germline OR Somatic BRCA1/2</td>
<td>Prior 2+ lines of chemo</td>
</tr>
<tr>
<td>Niraparib</td>
<td>n/a</td>
<td>Maintenance therapy for patients’ who respond to PARP or platinum</td>
</tr>
</tbody>
</table>
Summary: Hereditary Cancer Syndromes

• Many germline mutations are known to confer an increased risk for cancer.
• Each gene is associated with a specific spectrum of organs at risk and degree of cancer risk.
• More and more genes and syndromes are being discovered.
• A variety of resources exist to learn more about the common and more rare cancer syndromes.
Benefits of a Genetic Testing

- Increased likelihood of identifying mutation
- Learn risks for other cancers
- Opportunity for prevention
- Genetic testing for family members

IMPROVED PATIENT OUTCOMES
Thank You

FARR NEZHAT MD FACOG FACS

Medical Director, Nezhat Surgery for Gynecology/Oncology
Director of Division and Fellowship, Minimally Invasive Gynecologic Surgery and Robotics, NYU Winthrop Hospital
Clinical Professor, Obstetrics and Gynecology, Weill Cornell Medical College of Cornell University
Adjunct Professor, Obstetrics, Gynecology and Reproductive Medicine, Stony Brook University School of Medicine
Impact on Medical Management (BRCA1/2)

- Annual breast MRI beginning between ages 25-29, annual MRI and mammogram after age 30
- Consideration of risk-reducing mastectomy
- Recommendation of risk-reducing oophorectomy
- Male breast cancer and prostate cancer screening for male mutation carriers
- Consider screening for pancreatic cancer and melanoma in certain individuals
- Option of PARP inhibitor therapy for patients with advanced ovarian cancer
Colonoscopy beginning at age 20-25, repeat every 1-2 years

Consider risk-reducing hysterectomy and oophorectomy; timing individualized, but after completion of childbearing

Upper endoscopy every 3-5 years beginning at age 30-35 for patients with a positive family history of stomach and/or small bowel cancer or those of Asian descent

Consider annual physical/neurological exam beginning at age 25-30

Consider annual urinalysis every 3-5 years beginning at age 30-35 for patients with a positive family history of urinary tract cancers or those with an MSH2 mutation

Colonoscopy beginning at age 20-25, repeat every 1-2 years
Importance of Looking beyond *BRCA1/2* and Lynch for Hereditary Gynecologic Cancers

- **Ovarian Cancer Cohort (N=30)**
# Gynecological Cancer Genes Beyond BRCA1/2 and Lynch

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<th>TP53</th>
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<td><strong>Gynecological cancer risks and management</strong></td>
<td>Consider risk-reducing oophorectomy between ages 45-50</td>
<td>Consider risk-reducing hysterectomy for endometrial cancer lifetime risk ~28%</td>
<td>Possible increased risk for ovarian cancer</td>
<td>Increased risks for non-epithelial ovarian, cervical, and uterine cancers</td>
<td>~90% overall lifetime cancer risk, including gynecological cancers</td>
<td>Associated with rare ovarian cancer types</td>
</tr>
</tbody>
</table>
| **Other cancer risks and management** | Possible increased risk for breast cancer | Also associated with increased risks for breast, thyroid, renal, and colorectal neoplasms (benign and malignant) | Significantly increased risk for breast cancer | Also associated with increased risks for breast, lung, pancreatic, GI, and testicular cancers | Also associated with increased risk for breast & brain cancers, leukemia, sarcoma, others | **DICER1:** Ovarian sex cord-stromal tumors  
**SMARCA4:** Small cell carcinoma of the ovary, hypercalcemic type |
ATM
• Breast MRI beginning @ 40y

CHEK2
• Breast MRI beginning @ 40y
• Colonoscopy beginning @ 40y

PALB2
• Breast MRI beginning @ 30y
• Consider risk-reducing mastectomy based on family history

Lynch
• Colonoscopy every 1-2 years beginning @20-25y
• Consideration of oophorectomy and hysterectomy
• Screening for other tumors as indicated

Adapted from NCCN Guidelines V2.2017
NCCN Medical Management Guidelines for Genes Beyond BRCA

- **NBN**
  - Breast MRI beginning @ 40y

- **PTEN**
  - Mammography and breast MRI @30-35y
  - Risk-reducing mastectomy
  - Annual thyroid ultrasound

- **BRIP1**
  - Risk-reducing oophorectomy at 45-50y

- **RAD51C/D**
  - Risk-reducing oophorectomy @ 45-50y